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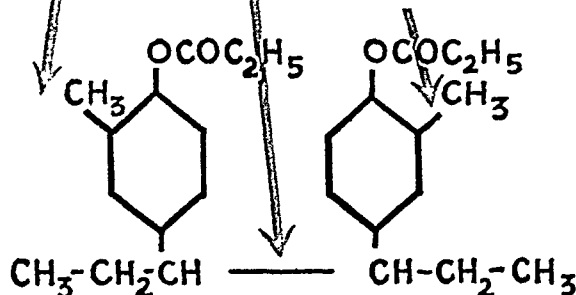
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(1) Sturgis, S. H.: Am. J. Obst. & Gyn. 53:678, April 1947.

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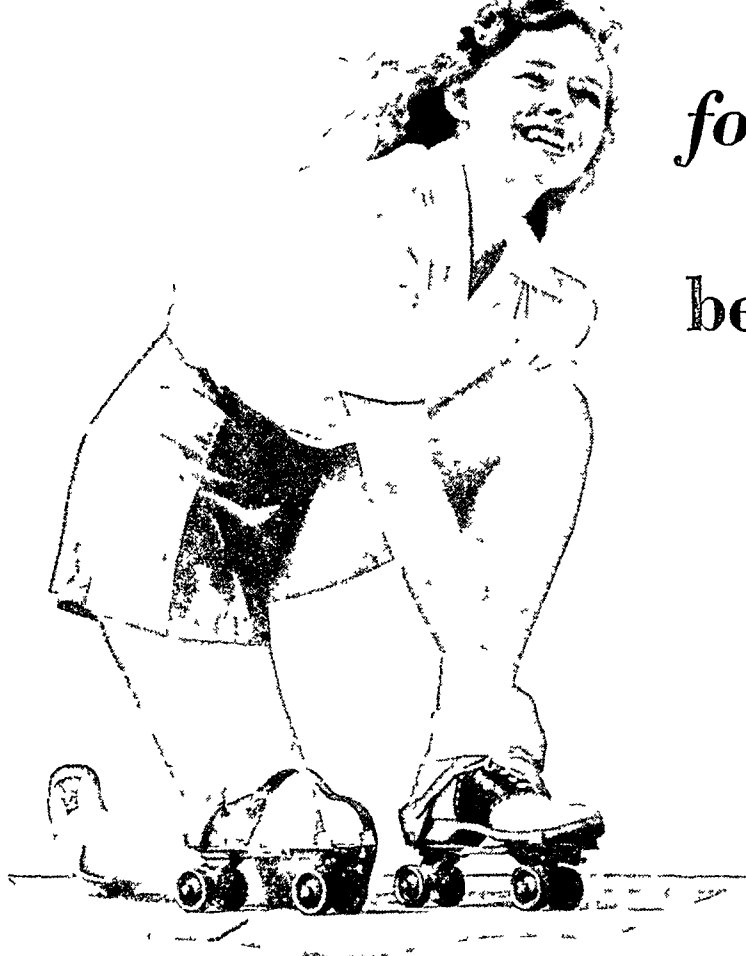
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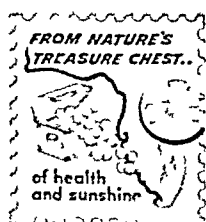
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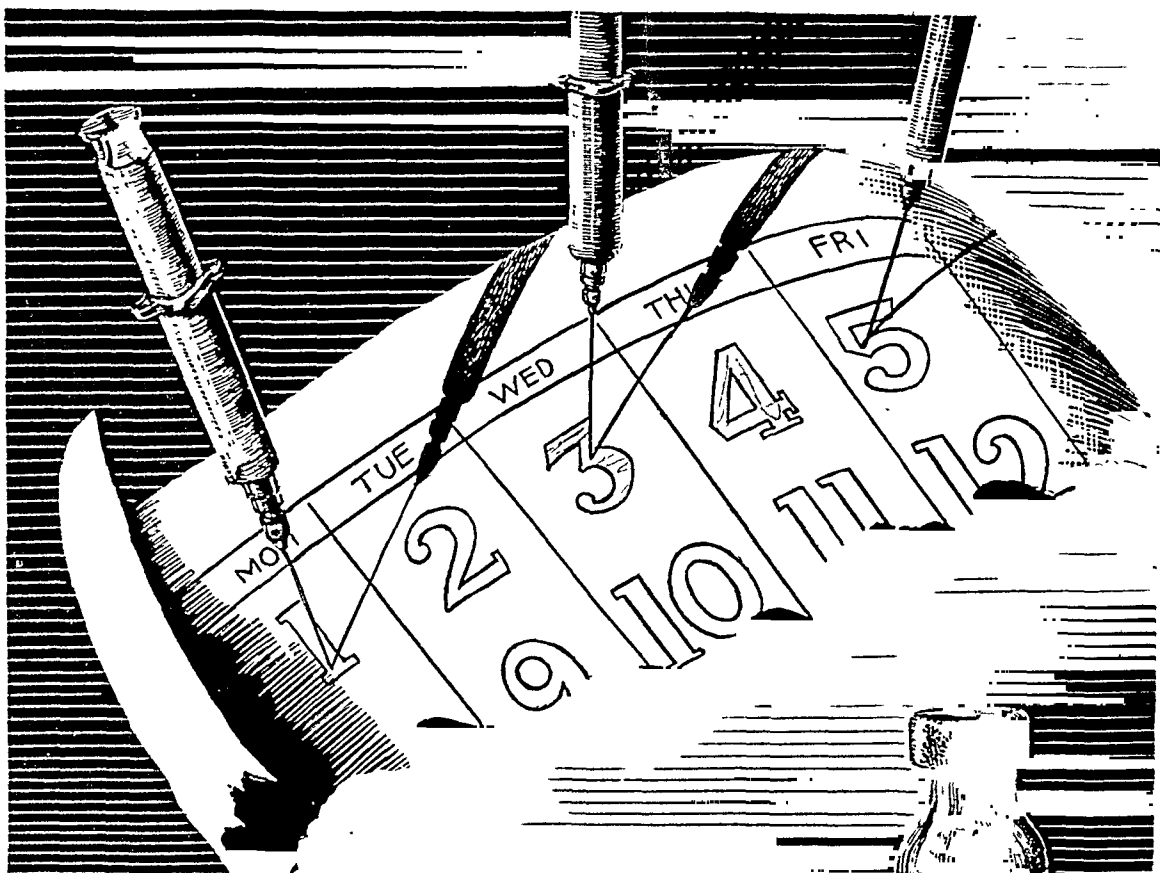
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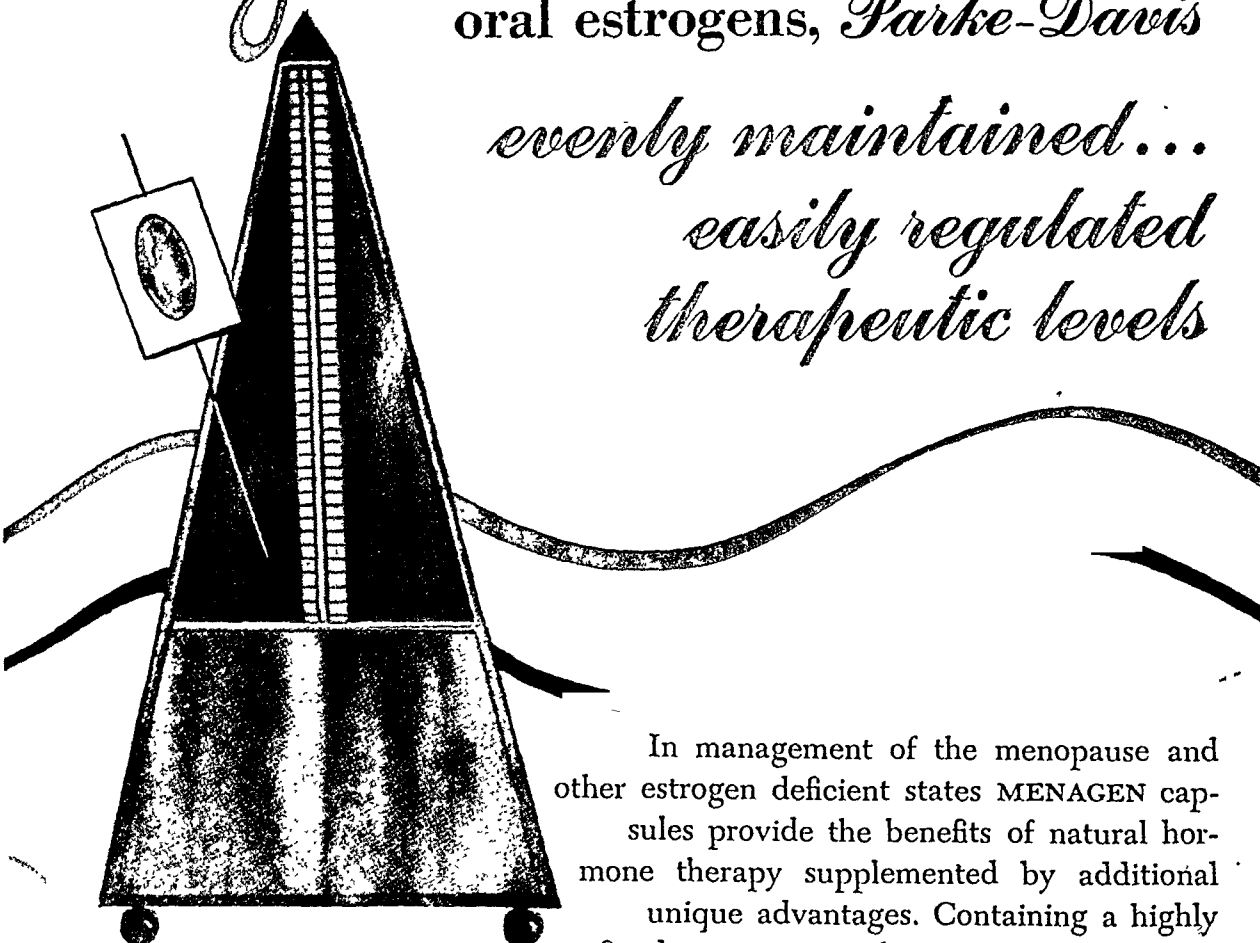
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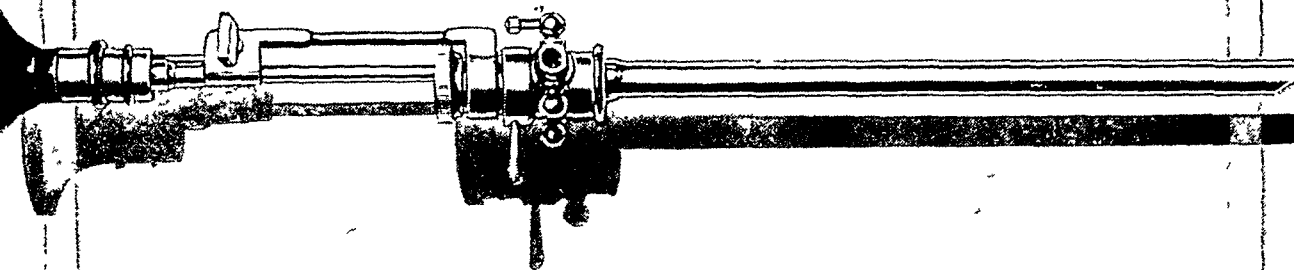
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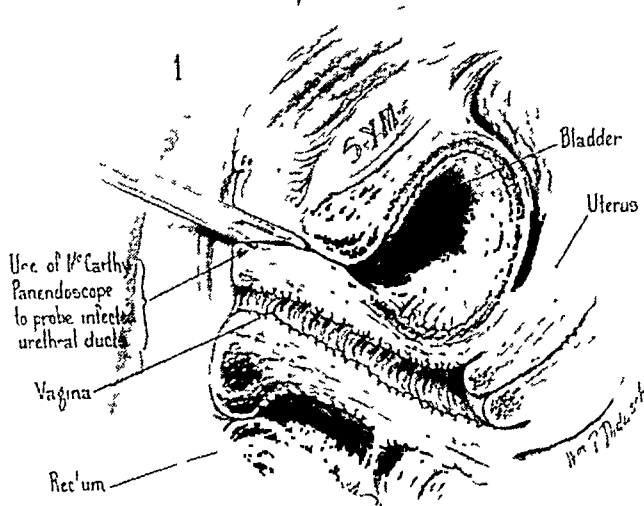
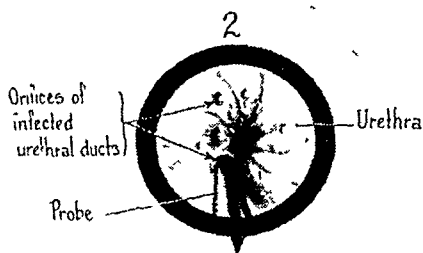


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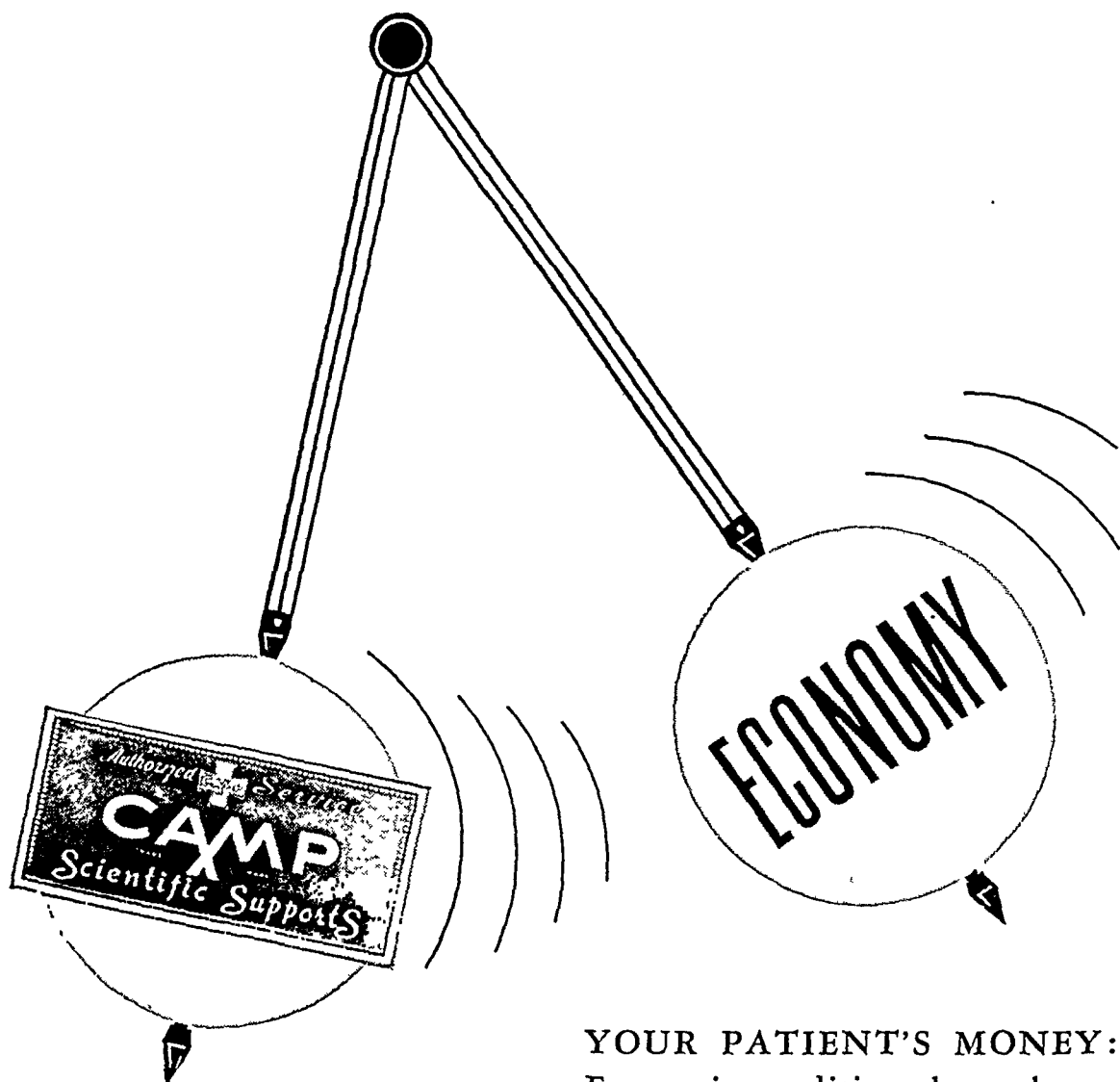
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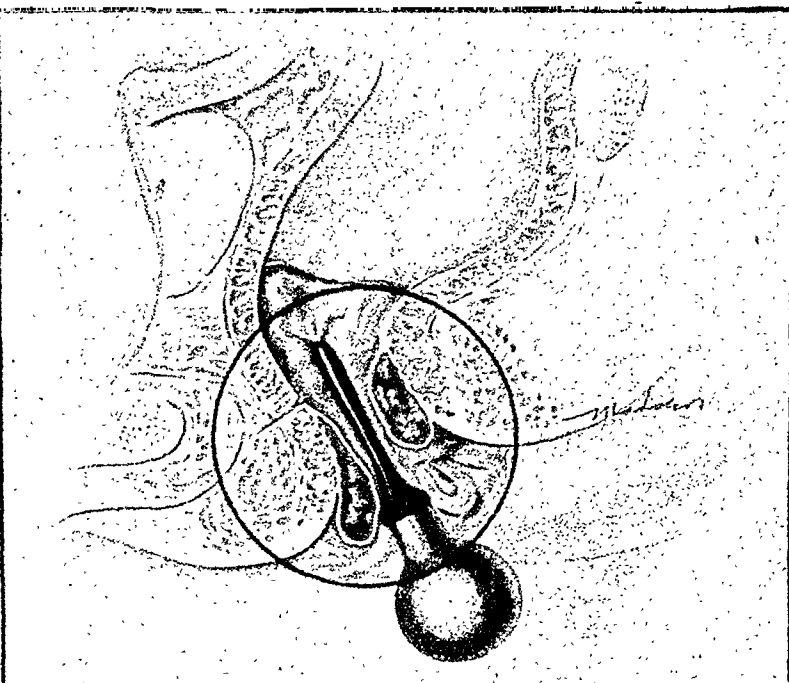
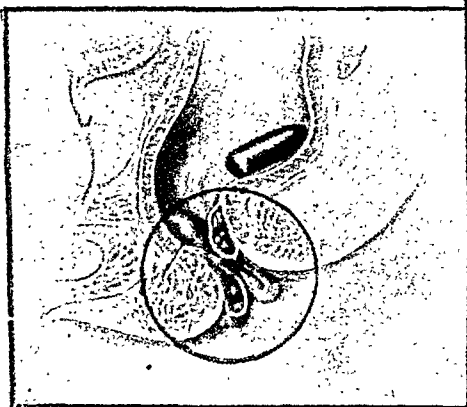
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Recent tests by an independent research chemist¹, compare Mennen Baby Oil and a commercial baby lotion, as to their penetrability by common infant skin irritants.

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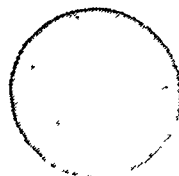
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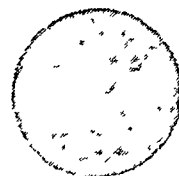
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Film of evaporated baby lotion (0.21 mm), 20,000 X. Note breaks, irregularity.



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- 1. Elsner, H.—A Method for the Study of the Penetrability of Liquid and Semisolid Films Used in Skin Protection. *Journal of Investigative Dermatology*, Vol. 10, No. 4, April 1948. Reprints upon request.
- 2. Schwartz, L., Mason, H.S., and Albritton, H.R.—A Method for the Evaluation of Protective Ointments. *Occupational Medicine* 1:376-385 (April) 1946.

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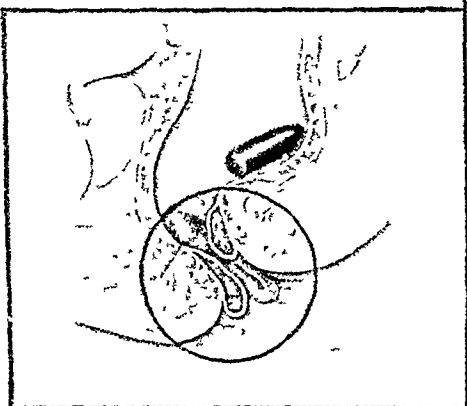
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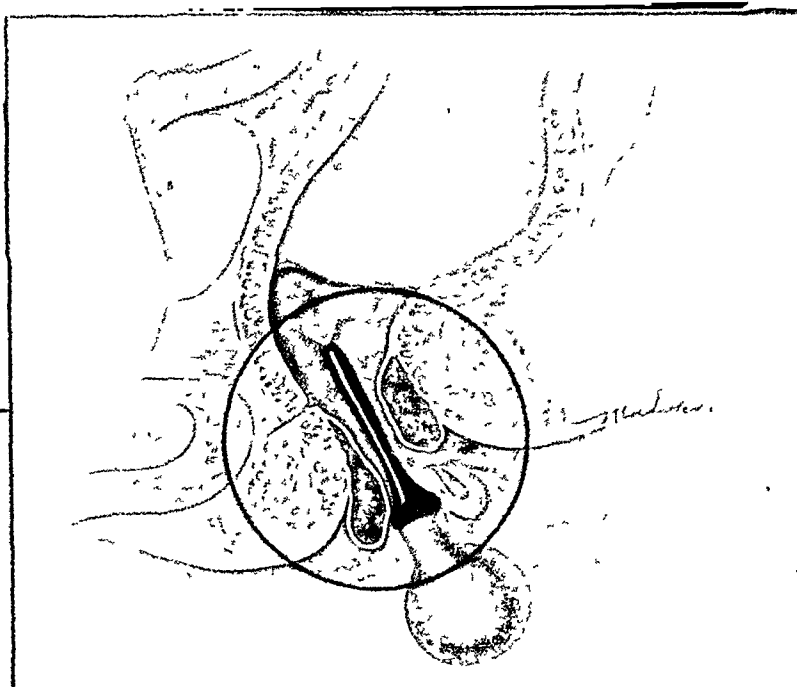
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¹Brown, W. E. & Bradbury, J.T.: Am. J. Obst. & Gynec. 53:749 (May) 1947.

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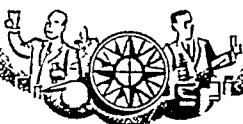
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May 24 to 26, 1948, at Williamsburg, Virginia*

ADDRESS OF THE PRESIDENT*

EMIL NOVAK, M.D., BALTIMORE, MD.

TO BE elected a Fellow of this Society is a great distinction, and one which can be attained by only a small fraction of the gynecologists and obstetricians of our own country and its good neighbor country to the north. To be elected its President is the highest honor which can come to any of us, and the deep appreciation, mingled with a sense of deep humility, which I myself feel must be the common reaction of every recipient of this honor. However I may feel about my inadequacy to fill a post once occupied by such men as J. Marion Sims and Thomas Addis Emmett, there is one point on which I yield to no one, and that is in my devotion to this Society and what it represents, as the emblem society of our specialty. Around it revolve the most pleasant associations of my own professional life.

As I mentioned in the few incoherent remarks of appreciation which I made at our last meeting, when still dizzy from my sudden and unexpected elevation to this pinnacle, there is no man in this Society whom I dislike, many whom I like very much, and not an inconsiderable group for whom I feel a deep affection.

Our last meeting was a most enjoyable and successful one, but it was marred by the fact that my distinguished predecessor in this office, Dr. Norris W. Vaux, was stricken with a serious illness shortly before the meeting. Both he and we were thus deprived of the privilege of having him occupy the presidential chair to which he had so deservedly been elevated, and which he would have filled with the efficiency, dignity, and charm so characteristic of him. We rejoice

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NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

that his health has been so much improved that he is with us again on this occasion, and I know how sincerely every Fellow of this Society hopes that he will grace our gatherings for many years to come.

During the past year, the shoulder tap of death has called from our rank three of our oldest and most respected Active Fellows: Drs. James R. Goodall, Curtis F. Burnam, and Henricus J. Stander. This is not the place to set forth their contributions to our Society or to our specialty, and this will be more appropriately done elsewhere in our Transactions. Suffice it here to say that their loss is deeply mourned by all of us, and that it leaves a painful gap in our ranks.

Equally heavy have been the losses among our Honorary Fellows since our last meeting, the list including two of our six American Honorary Fellows and one of the foreign group. Dr. Robert Meyer, whose epoch-making scientific contributions are known to all of you, died on Dec. 12, 1947. It was my privilege, at our meeting in Hershey two years ago, to present a biographical review of his life and works. Now that he has passed on, I am happy to think that some record of his career, however inadequate, is permanently inscribed in our archives.

Dr. Frank F. Simpson, who died on Feb. 10, 1948, played an active part in the life of our Society before his retirement many years ago, and was its president in 1917. He was secretary-general of the Seventh International Congress of Obstetricians and Gynecologists in 1912. Finally, the most newly-elected of our Foreign Honorary Fellows, Dr. Louis Carnac Rivett, the Foreign Guest at our meeting only two years ago, died on Sept. 10, 1947.

It is safe to say that no president of this Society has ever embarked on the preparation of his annual address without calling into consultation all the long line of his predecessors, through a review of all the presidential addresses of past years. Incidentally, such a review is highly educational, and it might well be made a required course of reading for all future presidents.

Just as much of the world's history consists of such periodically recurring events as wars, scientific discoveries, and religious upheavals, so have many of the fundamental problems of our specialty been with us since the founding of the Society and the address of our first President, Fordyce Barker. Much of this old wine has been put into new bottles by many of his successors. If it is true, as Sir Thomas Browne said, "that in seventy or eighty years one may have a curt epitome of the whole course of time," no president of this Society need go any further in his search for ideas than the addresses of his predecessors, especially if he feels no qualms at a bit of genteel plagiarism. For this he will have high moral support, for no less an authority than Emerson has said that "it has come to be practically a sort of rule in literature that a man, having once shown himself capable of original writing, is entitled thenceforth to steal from the writings of others at discretion."

In scanning previous presidential addresses, I have been interested to note how differently our presidents have interpreted their constitutional obliga-

tion to deliver an address at the annual meeting. Some have seized the opportunity to read papers on very specific scientific subjects in which they themselves were especially interested, with probably a fiendish glee that for once their remarks would not be curtailed by the sharp tap of the gavel made from Ephraim McDowell's door knob, always ruthlessly closing and never opening the door for prolonged discussion. This is a contribution of Ephraim McDowell which has never been sufficiently appreciated. Such a conception of the presidential address as I have described appears to be a rather selfish one, simply adding just another paper to an already heavily laden scientific program, without even the redeeming feature of the time limit imposed on other essayists.

Not a few of our presidents have chosen to devote their addresses to historical accounts of great events, great movements, or great personalities in the development of our specialty, and certainly no criticism can be made of the interest and the cultural value of such presentations. The same may be said of the few addresses which have gone rather far afield from our specialty into the realms of general science or literature.

The majority of past addresses, however, have been of general and composite nature, so much so that they have no titles, going down in our archives simply as "Presidential Addresses." They have dealt with all manner of topics of current interest and importance to the Society and the specialty, such as medical education, the proper training of those aspiring to be specialists, discussion and criticism of policies and trends, recommendations for the future, etc.

It is this concept of the presidential address which appeals to me as the logical one, the one intended by our Founders, and the one which might be expected to serve a real purpose, above that of a mere formal embellishment of our annual meetings. Such a concept would make the address similar in purpose to the annual Report to Congress by the President of the United States on the State of the Union.

If a title were insisted upon for such a simple and homely discussion of family matters, a tempting one would seem to be that of "A Fireside Chat," to borrow a designation made famous by the now silent golden voice which flowed so seductively over the ether waves only a few short years ago. I would, however, have to disclaim some of the original connotations of this term, for in our own small circle there have been no real or imaginary crises, there are no economic royalists to vituperate, and politics has never reared its ugly head in our midst.

But we have had our little family problems, and these should have made some impression upon those of us who have enjoyed Fellowship for many years. An address of this sort should, therefore, afford the President the opportunity of getting off his chest his reaction to some of the problems of the Society, although I must confess that I have nothing on my chest which has pained or oppressed me. While such pectoral purgations may be looked upon as largely excretory in nature, they may actually serve a fertilizing purpose, just as certain unmentionable excrementitious material may be transformed into the loveliness of a Chinese or Japanese flower garden.

I propose, therefore, to discuss a variety of topics, emulating the Walrus of Alice's Looking Glass, in the familiar lines:

“The time has come, the Walrus said,
To talk of many things;
Of shoes and ships and sealing wax,
Of cabbages and kings.”

A useful recipe for the preparation of an address of this sort, and you will find it equally serviceable in the concoction of commencement addresses, extemporaneous after-dinner talks and other such purposes, would seem to call for the following ingredients:

1. A wise and well-tempered discussion of the various topics which have been selected for the body of the address;
2. A sprinkling of classical and literary allusions to indicate the breadth and depth of the speaker's cultural attainments, and
3. A dash or two of purported wit to lighten the profundity of the discourse. I am afraid that, like the corner groceryman, I am “just out” of some of the necessary ingredients, so that the resulting brew may leave something to be desired.

Each year our Society receives an invigorating infusion of new blood, through the election of a number of new Fellows, and it is the caliber of these new recruits which will determine the future standards of our organization. Our Council has no more important function than the careful screening of the candidates who come before it for consideration. The stated policy has always been the preliminary selection of a group of potential candidates who are then invited to participate in the formal program of the succeeding meeting. The latter is a wise provision, since it gives the opportunity of personal evaluation of possible candidates. However, it has always seemed to me that there are two possible points of weakness in our present method of procedure.

First of all, those who are formally listed as invited guests and potential candidates are usually nominated by individual Fellows. Certainly no Fellow should be deprived of this right of nomination, but the final selection of candidates should not, it seems to me, be limited to these individual nominations. The Council should be given the authority, which it does not now have, to go out into the open market, and this right should be exercised as a formal policy.

According to our present Constitution, candidates for Fellowship “shall be proposed to the Council by two Fellows only, who are not members of the Council, at least two months before the first day of the meeting, etc.” This prerogative should be continued, but in addition, the Council should be privileged to bring to the Society's attention the names of other worthy candidates, who are easily overlooked if they do not happen to have a friend at court. It should be empowered to pluck the fairest flowers that bloom anywhere in the country, and not only those which happen to grow in some Fellow's backyard. It is easily conceivable that young men of great promise or of already proved accomplishment might never otherwise be brought to the Society's consideration,

“Full many a gem of purest ray serene
The dark unfathomed caves of ocean bear;
Full many a flower is born to blush unseen,
And waste its fragrance on the desert air.”

Secondly, the introductory paper or discussion required of potential candidates should not be given undue weight in the consideration of the candidate's qualifications. Even the veriest neophyte, with such an incentive as possible Fellowship, might conceivably produce an outstanding contribution, and still fall short of proper standards for admission. By the same token, men who, by virtue of their teaching positions and their professional stature, were clearly qualified for Fellowship have on more than one occasion presented very undistinguished or even poor introductory theses. In the latter case, the Society as a whole has always, so far as I recall, recognized the Homeric nodding in such presentations, and has looked beyond them to the already demonstrated worth of the candidate.

Again, it should not often be necessary for our Fellows, in looking over our programs, to ask “who is this man who is reading a paper on such and such a subject?” Most of our candidates should be men who through their accomplishments and their publications have already stamped their names on our minds. Being now a member of the Council and knowing how conscientiously it guards the gateway of admission to the Society, I feel all the freer in making these comments.

It is gratifying that our Society has within recent years shown a tendency to admit to Fellowship an increasing proportion of comparatively young men who had already given clear indication of actual or potential leadership in our specialty, thus creating a healthy balance between the mental alertness, elasticity, and enthusiasm of youth on the one hand, and the maturity, balance, and allegedly greater wisdom of those no longer young. As the garrulous but lovable Autoerat said, “New ideas do not build their nests in old men's brains, and the first whisperings of truth are not likely to be heard by those who already feel the need of an ear trumpet.”

On the other hand, it is more common in the young than in the old for the mind to function like a sponge, sopping up new knowledge indiscriminately, and giving it off in great profusion on the slightest squeeze. Without the slightest attempt at generalization, which would of course be ridiculous, the minds of more mature men are more likely to develop sievelike characteristics, sifting out the knowledge which can be actually utilized. This is another way of expressing the aphorism that “knowledge comes, but wisdom lingers.” In any event, I do believe that our older men are likely to have lost a good deal of the charming credulity so characteristic of our profession, and to have developed some degree of healthy skepticism toward many of the superficial new ideas of one sort or another which each year brings. Some of these die a-bornin', some die quickly and are soon forgotten, but still others may get such a foothold that many years are required to dislodge them.

The above remarks will be put down, probably correctly, as the prejudiced ramblings of one who can no longer consider himself young. They started off

quite innocently with the simple observation that our Society represents a happy mixture of the young and those not so young, that we shall have to depend upon the former to carry our standards into the years of the future, and upon the latter to act in a steadying and comforting capacity, like the convenient scratching-boards which give solace to the cattle in the pasture. To put in a final lick for my older colleagues, they may, at any rate, like peaches or bananas, be expected to become mellowest and sweetest before they decay.

In the scientific world, as in the social world, the oldsters might just as well reconcile themselves to the fact that they must, in their own clumsy and creaking fashion, adapt themselves to the ways of the younger generation among us, and not vice versa. During the restless years between the two World Wars, many an anxious parent had serious misgivings as to the fate of the youngsters of those days, who succumbed so easily and often so enthusiastically to the temptations of cocktail parties, who in their dancing hours took up where their parents left off, and who dashed about the countryside in fancy roadsters or collegiate jalopies.

The later history of this particular young generation has shown conclusively, I believe, that our grim forebodings were not warranted, and that such fundamental American attributes as initiative, resourcefulness, and courage were not affected by such passing phases as I have mentioned. It was these very qualities in many millions of our young people which brought us safely through the recent war holocaust, and it is to them that we must look for the ultimate reconstruction of a brave new world from the battered old globe we are turning over to them.

In our own profession, however, and in the narrower field of our own specialty, the older generation need make no apology for the legacy it is leaving to its successors. Moreover, the older Fellows of this Society, raised in a purely clinical era, deserve much credit for learning the new vocabularies which have marked the development of our knowledge, especially in the fields of pathology and endocrinology, not to speak of the new fields of obstetrical immunology and chemistry.

It is my impression that the older members of our profession have found it more difficult to reconcile themselves to the changing order in medical education, and not a few continue as die-hards in this respect. In a not so remote day, the men on whom professorships were bestowed were those who had achieved clinical maturity and eminence, and who were ordinarily as mature in years as in experience. Such appointments now go to young men selected because of their scientific promise, which with much justice is considered a far more desirable asset than the more readily acquired clinical experience. There are many who still think that a happier compromise could be struck than has yet been reached, but the newer surge has become so strong that it cannot be gainsaid, and it will probably justify itself. In this respect, the older generation has bowed gracefully to the new order, just as it has accepted the closely related policy of full-time professorships, which for so long divided our profession, and which is still viewed with dubiousness by some in our ranks.

Not much more than a generation ago, the specialists in our own and other fields were largely self-trained, many of them entering the specialty through the gateway of general practice. This fact was recognized by the American Board of Obstetrics and Gynecology in its earlier years, and provision was wisely made for the certification of applicants thought qualified by years of practice in the specialty, even though they were lacking in the years of formal training now required of all candidates. No longer should a man expect to learn his specialty by the method of trial and error, as did the famous ophthalmologist who confessed that he had spoiled a whole hatful of human eyes before he perfected himself in the cataract operation.

The Board has made a notable contribution to the postgraduate training of obstetricians and gynecologists and to the elevation of standards of specialization in this field. It has no doubt made some mistakes, and it would be strange if all its policies and aims met with universal approval, but on the whole it is doing a much needed job and doing it well.

Having as an Associate Examiner assisted in the conduct of a number of the Board examinations, I have been deeply impressed with the unselfishness of the Board members in giving so generously of their time and effort in carrying on their really arduous work, and of the idealism and sincerity of the Board's purpose. It is not invidious to emphasize especially the long years of faithful service rendered by the Chairman of the Board, Dr. Walter T. Dannreuther, and the Secretary, Dr. Paul Titus.

Whatever the older men of the profession may think of the Board's work, although even these must now be convinced of its value, the young men throughout the country have made Board certification their first big objective after completion of their training. This has inevitably impelled them to seek their training in hospitals approved by the Board, and thus has immeasurably improved the quality of service in hospitals desirous of securing approval for postgraduate training in obstetrics and gynecology.

It is difficult, probably even for the Board itself, to prophesy its ultimate effect upon the development of our specialty, but few will doubt that it is moving in the right direction. It has publicly disclaimed any advocacy of a policy that Board certification be required of those holding senior hospital staff appointments, and yet just this policy has already been adopted by some of the hospitals in this country, with often resulting rancor and discontent among the staffs of such hospitals. Indeed, it is not rare to hear reports of discontent among residents because their chiefs are not Board diplomates, and one gets the impression that some hospital residency tenures are looked upon merely as opportunities for putting in the requisite number of years and cramming for the Board Examinations, rather than in broad and systematic training for the specialty. These are disadvantages which will in time correct themselves, and they do not, in my judgment, reflect upon the wisdom of the Board's fundamental goal of raising the standards of practice in obstetrics and gynecology.

The World War has greatly intensified a problem which had already been evident, that of the difficulty faced by young men who aspire to enter our specialty of obtaining opportunities for the special training required by the

Board. The simple fact is that there are not enough posts of this kind available to take care of the large number of deserving young men anxious to train themselves as specialists. This is true in spite of the helpful policy of a good many hospitals in increasing the size of their resident staffs. The condition will probably improve somewhat after the backlog of returning veterans has been taken care of, but the general problem will still remain. It has been necessary to make use of the preceptor system as a supplement to more formal training, but this is probably to be looked upon as a necessary but far from ideal makeshift.

The chief hope would seem to lie in an increase in the number of hospitals qualifying themselves for Board approval. As the number of Diplomates will steadily increase, and as these will in the future increasingly dominate the hospitals which they will staff, there is all the more reason to expect a steady increase in the number of hospitals offering a satisfactory type of training.

An even greater need for postgraduate instruction has become apparent in the past few years through the influx of large numbers of foreign physicians who are seeking postgraduate instruction in our clinics. The world leadership in medicine which Germany had so long held had been slipping from her grasp a good many years before World War II, but its fall was precipitate with the rise of Nazi power. Government-inspired studies in *Rassenhygiene*, always demonstrating the supremacy of the pure Nordic blonde, were sorry substitutes for the substantial and often brilliant scientific output which made the Germany of a preceding generation the Mecca of medical men from all over the world.

Leadership is now in our own hands, and there is little doubt that here it will remain for many years to come. We can well be proud of the accomplishments which have given American medicine this world supremacy, but if we are to be the teachers of the world, we must develop a much more elaborate machinery for postgraduate instruction than now exists. Many of our leading medical schools have had practically no machinery of any sort except that represented by the postgraduate training of hospital and resident staffs. Foreigners visiting our clinics are likely to be received courteously and they are made welcome to observe the work of the clinic, but without any attempt at formal instruction.

Such visitors are now flocking to us in ever increasing numbers, especially from the Latin-American countries, but with many also from both Europe and Asia. Many of them are satisfied with the crumbs which they can pick up by superficial observation of the work of perhaps many clinics, just as many Americans in a former day were content with similar superficial visits to the German medical centers. Even such visits as these had their value, if for no other reason than that they gave some idea of the atmosphere of the German clinics, and the opportunity of seeing and hearing some of the great masters of the German medicine of that day.

I am sure that a considerable proportion of the older men here present treasure the memories of such visits, and of having had at least some contact with such personalities as Bumm, Stoeckel, Meyer, Franz, the Landau brothers, Strassman and Ludwig Pick in Berlin, and with other such leaders as Schröder, Döderlein, Sellheim, Wertheim, Schauta, Halban, Menge and many others whose names will long remain in the literature of our specialty.

Such visits had a collateral cultural value, for the work of the American "student" was rarely taken so seriously that it interfered with sightseeing, visits to cathedrals and art galleries, and, last but not least, many delightful sessions in the very "gemüthlich" atmosphere of the fine beer gardens of all the German cities. These were often enriched by extracurricular discussions with the younger members of the teaching staff, always willing to give their all for a good meal and a few steins of beer.

On the other hand, it must be admitted that certain of the very poorly paid *privat-docents* were far more mercenary, giving of their knowledge only at so much per hour. This was only a reflection of the general European attitude toward Americans, all of whom were of course fabulously rich according to the European concept. Even in those days, the traveling Americans contributed generously to European economy, an American role which has been blown up to colossal proportions by the two World Wars. It would almost seem that two totally different words which sound alike, "succor" and "sucker," have come to mean about the same thing.

While perhaps the majority of American visitors to the German clinics of a former day belonged to this butterfly type, which flitted from clinic to clinic, taking dainty sips of whatever each one offered, there was a minority of more serious students who dug themselves deeply and for long periods of time into those clinics which could offer them what they wanted. One has but to consider the lives of such men as Welch, Halsted, Cushing, and a whole host of other American medical leaders to appreciate the full force of the German influence to which they exposed themselves in their formative years.

This German influence forever afterward colored the lives of these men, and through them and through the successive generations of men whom they themselves trained, it undoubtedly played an important part in the steady and rapid development of medical education in our own country. For example, I believe it can be shown that the Flexner report of 1910, commonly looked upon as marking the end of the era of proprietary medical schools and diploma mills and the beginning of the modern era in our medical teachings, stems directly from a group of men who were ambitious to emulate the then unexcelled German system.

We should not be ashamed to acknowledge this debt we owe to the German medicine of the pre-Nazi era, however much we may deplore its later débacle, and however much we may pity or even despise the German people, including many of our own profession, for their blindly enthusiastic participation in the Hitlerian orgy.

A review of the Transactions of this Society must impress one with the generally high standard of the hundreds of scientific papers embodied in them, and of the contributions which this Society has made to the literature of our specialty. On the other hand, it will probably be disillusioning to one who seeks for contributions which might be considered of epoch-making importance. In the nearly quarter century covered by my own active membership I can, as a matter of fact, think of only two contributions by Fellows of this Society which

would unquestionably be accepted as "outstanding advances," or, to use a much abused designation, "discoveries."

One of them is the important contribution of the late John A. Sampson in establishing pelvic endometriosis as an important and frequent pathologic and clinical entity. The other is the introduction of tubal insufflation by I. C. Rubin, representing as it does the most important advance of our generation in the study of female infertility. Even if one looks back over a much longer span, to the very inception of the Society, a similar paucity of really historic contributions is revealed. I hasten to add that this comment is not to be interpreted as reflecting on the scientific fecundity of this Society, but rather to impress the fact that, while the literary mills grind on in our specialty as they do in all fields of medicine, and while every year many papers appear which add scattered bits to our knowledge of obstetrics and gynecology, one can hope for only an occasional forward thrust of the frontier of knowledge of clear decisiveness and importance.

After all, discoveries cannot be pulled out of thin air. I have a friend, a distinguished scientist, with whom I occasionally had luncheon in his laboratory when he was in Baltimore, and who, when one o'clock came, would often pull out his watch and exclaim, "My goodness! Time to go upstairs and make another discovery!" Rarely does a discovery come crashing into the brain like a bolt from the blue. More often, it is the final culmination of the long and painstaking work of many years, not only on the part of the discoverer himself, but also of many other investigators in many lands and going back many years. Advances in knowledge are usually achieved by this building-block method, only the gleaming capstone being placed by the man whom the world acclaims as a genius. As Edison says, genius is composed of only about 2 per cent inspiration and 98 per cent perspiration. The really productive investigator must have imagination and vision, as well as the ability to sift out from the work of those who have gone before him the shiny fragments which denote rich scientific potentiality. But beyond this rare gift for selecting the direction of his own research, and perhaps it is this which constitutes the real "divine afflatus," there is then required a period of long and intensive effort which may stretch over many years.

The research man works with his problem, sleeps with it, and dreams of it, so that he becomes a veritable scientific monomaniac. To illustrate, once Sampson had gotten his teeth firmly into the endometriosis problem, all of his subsequent papers during the twenty-five years before his death dealt with the same disease, except for a small group on another subject, obviously stemming from his studies on endometriosis. In the same way, only a small proportion of Rubin's numerous papers since his introduction of tubal insufflation in the study of sterility, something like 10 out of 69, have dealt with subjects other than sterility and tubal insufflation. This does not by any means indicate that these men had single track minds, for both were men of broad gynecologic training, with an interest in all gynecologic problems. It means simply that concentration of effort was necessary for the establishment of the advances for which they are responsible.

Many sins are committed in the name of research, the desirability of which we are constantly preaching to our younger men. Laudable as this inspirational propaganda is, it no doubt explains the enormous annual spate of mediocre publications, since many appear to have the naive idea that writing and research are more or less synonymous. The dictionary definition of research as a "critical and exhaustive investigation or experimental study having for its aim the discovery of new facts and their correct interpretation," indicates that it is made of much sterner stuff.

Only a small fraction of medical papers represent true research, and yet the fact remains that a large proportion of them serve a valuable purpose in refurbishing established knowledge in newer or more attractive or more forceful form, and every pedagogue knows that reiteration is an indispensable asset of good teaching. In a broad sense, such publications can be considered a very important part of the postgraduate training of both the author and the reader. No one profits more from a paper than the author thereof. There is much truth in the old saying, "if you don't know anything about a subject, write a book about it." The only trouble is that sometimes readers of such books lay them down with the feeling that the author still knows very little about his subject.

The longest journey begins with a first step, and the first literary step may be halting and uncertain. It may take the form of case reports, and even those are not always to be scoffed at. Or the young author may very early show a statistical bent, though this is not likely to result in papers of great glamor. This statement probably expresses a personal prejudice on my part, since, with full appreciation of the value of statistics of the proper sort, I happen to be one of those handicapped individuals who shudder at the sight of long columns of figures, plentifully interspersed with decimal points and even an occasional logarithm, and who grow dizzy following the ups and downs of the beautiful graphs adorning many of these statistical papers. Still others of the neophytes early show an interest in the pathologic, or the chemical, or the bacteriologic, or the radiologic aspects of their work, and such early interests are not infrequently indicative of the later special professional interests of such men, as amply illustrated in our own Society.

It is only natural that most of those who write on gynecology and obstetrics in our country seek an outlet in the only American journal of national scope devoted exclusively to our specialty, and the able editor of that JOURNAL is hard put to it to find space to take care of this output without unreasonable delays in publication of his material. But it would not be fair for the editor to be too hardboiled in the rejection of papers just because they do not show impressive originality or because they emanate from men whose names are as yet unknown to us. Often they are young men just trying their literary wings, and they deserve the encouragement which they get when they see their names in print for the first time. Among them will be some of the future leaders of our specialty. While this problem of providing proper outlets for the ever increasing literature of our specialty has been the subject of considerable discussion, and while it has also been considered by your Council, the feeling has been general that the official organ of our Society has, under the long and able editorship of Dr. George W. Kosmak, rendered an outstanding service to our specialty.

To revert for a moment to the subject of medical research, there are other aspects which have disturbed a great many of us. In his address at the opening of the Banting Institute in 1930, the late Lord Moynihan stirred up a hornet's nest by lamenting the fact that so much of the research carried on in medical institutions is directed to problems which can scarcely be considered to have any bearing on human health and disease. He also bemoaned the fact that mice and rats received too much attention from investigators, and that too little is given to the human being who, after all, is a very readily available animal suitable for at least some types of experimental study.

It is obvious that hominal research, as Moynihan called it, has very sharp limitations, even though there is some reason to feel that it has not been as richly developed or as highly organized as has been the experimental laboratory study of the lower animals, which has yielded so large a proportion of the really outstanding advances in medical science. It is easy to understand the rather violent reaction created by Moynihan's criticism among those working in the field of medical research, although it may still be true that those working in medical research laboratories do not devote a sufficiently large proportion of their efforts to problems with clearer and richer potential application to human health and disease.

There are other so-called "researchers" who appear to delight in setting up men of straw and then knocking them down with great gusto. They spend much time and money in proving figuratively, that the moon is not made of green cheese. The world's reaction is likely to be "Cui bono?" which, in loose translation to good American slang, would be, "So what?"

These somewhat flippant comments are made simply to emphasize the fact that not all research is intelligently conceived or prosecuted, and that a considerable fraction of it is of that spurious brand to which our late enemies, the Germans, applied the expressive designation of "*Scheinwissenschaft*."

No one has more beautifully allegorized the never-ending quest for truth than Milton, who relates that the lovely form of the virgin Truth was hewn into a thousand pieces and then scattered to the winds. Since that time mankind has been searching for these fragments in all corners of the earth and in all fields of science. Those fragments bearing on human health and disease are most likely to be discovered by medical investigators, just as physicists and chemists are more likely to find the fragments bearing on their own sciences. But there is no law against the trade and barter of fragments when these can be better utilized in other fields. To mention the most outstanding example, the discovery of radium by the Curies, in the field of physics, has been the means of saving many lives when applied in the field of medicine.

It would be tempting, if time permitted, to discuss some of the important clinical problems with which our specialty is concerned, and especially that of cancer, still the ruthless destroyer of so many of the women committed to our care. Suffice it to say that now, and for the first time, the warfare against cancer has assumed all-out proportions. Not only our own profession, but scientists in every other field are now enlisted in the cause—pathologists, chemists, endocrinologists, physicists, botanists, and geneticists. Nothing is more certain than that

the riddle of cancer will be solved, possibly in the not-too-distant future, and it is even possible that a cure will be discovered before the cause of the disease is revealed.

In the meantime, substantial if not brilliant gains in the salvage from the disease have been made by both radiotherapy and surgery. Most of us must feel that both of these, in spite of their accomplishments, are to be looked upon as make-shifts, often effective, until some more specific plan of treatment is discovered, something comparable in the life-saving field to the atom-bomb in the destruction of life, though not necessarily, of course, related to the application of atomic energy. If I were anxious to perpetrate a particularly pernicious pun, I could say that the salvation of the daughters of Eve does not necessarily depend upon the behaviour of an atom.

The limit of membership in our Society was originally fixed by our Founders at sixty, and it was not until the presidency of J. Marion Sims in 1880, and at his instigation, that this limit was raised to one hundred, where it remains today. From time to time one hears the criticism that it is too low, in view of the enormous increase in the number of those now specializing in obstetrics and gynecology. I do not believe that this argument is sound, or that it would appeal to many members of our Society. If the number of specialists has greatly increased, so has the number of special societies, national, regional, state, and local. No man of merit can justly complain of the lack of a forum.

The fact that hundreds of obstetricians and gynecologists will never attain Fellowship in the American Gynecological Society indicates no snobbishness on the part of the latter, and no lack of receptiveness to those who loom clearly above their fellows. By the very nature of the stated standards of this Society, it must be an exclusive organization, using this term in a scientific and not a social sense. Furthermore, a much larger membership would mean the end of the pleasant and intimate gatherings which we now enjoy, usually under one roof, and in extremely agreeable surroundings. And it is just this intimate personal contact which is an outstanding charm and asset of our meetings. This would be sacrificed in the more hurly-burly type of meetings which a much larger attendance would entail.

On the other hand, I do believe it is always desirable to keep our meetings open to a limited number of guests, above those formally invited to participate in the scientific programs as potential candidates. A total attendance of two hundred or perhaps somewhat more would not rob our meetings of any of the advantages mentioned above, and it would extend to our guests the opportunities for personal contacts which have been stressed. A scientific paper can be read if it is not heard, but a hearty handshake, a game of golf, a pleasant and intimate chat at the luncheon table or in the rathskeller, all these involve close personal relationships far more indelible than the written word alone. It was Woodrow Wilson who said "I would never read a book if it were possible for me to talk half an hour with the man who wrote it." I shall always treasure the memories of the personal contacts and the friendships with many of the great men of our specialty which were made possible to me by our annual gatherings.

One need not need be a hero-worshipper to derive a thrill from the mere touch of the hem of the garment of greatness. The man who saw Lincoln and who heard his Gettysburg Address remained thereafter a rather hallowed individual. After all, the things which make a man great are not merely what he writes, but also how he lives, thinks, reads and feels. What he writes may live after him, and make him great in the eyes of the world, but the other traits too often are interred with his bones, though they may explain his greatness to those who knew him when living.

The end object of most men's lives is happiness, but there are wide individual differences in their concepts as to what constitutes happiness. To some it connotes wordly success, and the common fate of these is disillusionment. No work of art has ever impressed me more than a small bronze statue by the great Rodin in one of the galleries in Paris. It was, as I recall it, entitled Success, and it represents a man toiling up the steep side of a mountain. His haggard, tired face has just reached the top, and there he sees before him, the fruit of success, a pile of dead men's bones and ashes.

There are others who deliberately seek fame and greatness, forgetting, as our own John Hunter said, that "no man who wanted to be great ever was a great man." That most delightful of epigrammatists, Oscar Wilde, put it even more neatly when he said that "there are only two great tragedies in life, not getting what you want—and getting it!" It is what we see and do and feel during the whole journey of life that counts, and not the mere goal, just as the traveler gets his joy out of the scenery and the people he encounters rather than in merely reaching a certain destination. "To travel hopefully is better than to arrive."

It may seem like a profligate doctrine to urge that the greatest happiness and the greatest chance for real success is likely to come from living each day for itself, with not too much thought of the morrow, as Sir William Osler was so fond of preaching. If one has found a niche in life which he enjoys, as is true of practically all medical men, and if he is happy in his home life, his family, and his friends, he will accumulate a vast capital of happiness during his lifetime, and incidentally a modest or a great measure of what the world calls success.

Since I have, in keeping with my duly announced plagiaristic policy, borrowed a thought from the philosophy of William Osler, it may not be inappropriate to conclude this address with a fuller quotation from that beloved physician as to his ideals of life. Incidentally, I would commend this to you as a more realistic expression of the lofty ideals of our profession than is found in the archaic Hippocratic oath which has been repeated mumblingly by so many generations of medical graduates.

"I have three personal ideals. One to do the day's work well and not to bother about tomorrow. The second ideal has been to act the Golden Rule, as far as in me lay, toward my professional brethren and toward the patients committed to my care. And the third has been to cultivate such a measure of equanimity as would enable me to bear success with humility, the affection of my friends without pride, and to be ready when the day of sorrow and grief comes to meet it with the courage befitting a man."

THE PRESENT-DAY STATUS OF NONINVASIVE CERVICAL CARCINOMA*

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FOUR years ago we¹ presented before this Society a paper which concerned itself with the minimal histologic changes in the cervical biopsy which would justify a diagnosis of carcinoma. Our observations followed those of Schottländer and Kermauner,² who noted a thin layer of carcinoma extending over the surface, surrounding advanced cervical cancer. They also followed the epochal work of Schiller,^{3, 4} who first conceived the idea that surface carcinoma could be the beginning of invasive cancer. He described many cases without evidence of invasion in which cellular changes in the surface epithelium were found that were identical to those of invasive cancer. When we undertook our study it appeared to us that there was not sufficient evidence in the literature to justify completely the belief that these intraepithelial changes were precursors of invasive cervical carcinoma. To elucidate this point, we made a comparative histologic study of the biopsy specimens showing malignant changes in the surface epithelium and the ultimate specimens of the cervixes removed at hysterectomy. The cervixes were cut into several blocks and sections made from different levels in a search for evidence of invasion. In fifteen of the sixteen cervixes removed, histologic evidence of invasion was found.

Since our publication of 1944, we have continued to collect histologic and clinical evidence concerning this subject and it would seem that we have amassed sufficient data to crystallize our ideas on diagnosis and treatment. This paper is presented before this Society to give our conclusions based on a much wider experience and also with the hope of stimulating discussion concerning this subject.

The histologic picture of "intraepithelial carcinoma" or "carcinoma in situ" has become reasonably familiar to all those interested in gynecologic pathology. Figs. 1 and 2 are typical examples. There is a loss of normal stratification of the epithelial cells, variability in the size and shape of the cells, nuclear hyperchromatism, and a frequency of mitotic figures. In short, the cellular changes are identical to those of invasive cancer and, indeed, metastatic cancer. Schiller has described an abrupt, oblique line of demarcation between this abnormal surface epithelium and the normal stratified epithelium. Although we have seen such an oblique line (Fig. 3) many times, we have also seen an abrupt perpendicular change (Fig. 4) and the transition from abnormal to normal cells is often gradual.

Our observations lead us to believe that cervical carcinoma begins in the basal layer of the portio vaginalis and that slight changes in this layer may be the precursor of intraepithelial carcinoma. We have seen repeatedly in biopsy

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

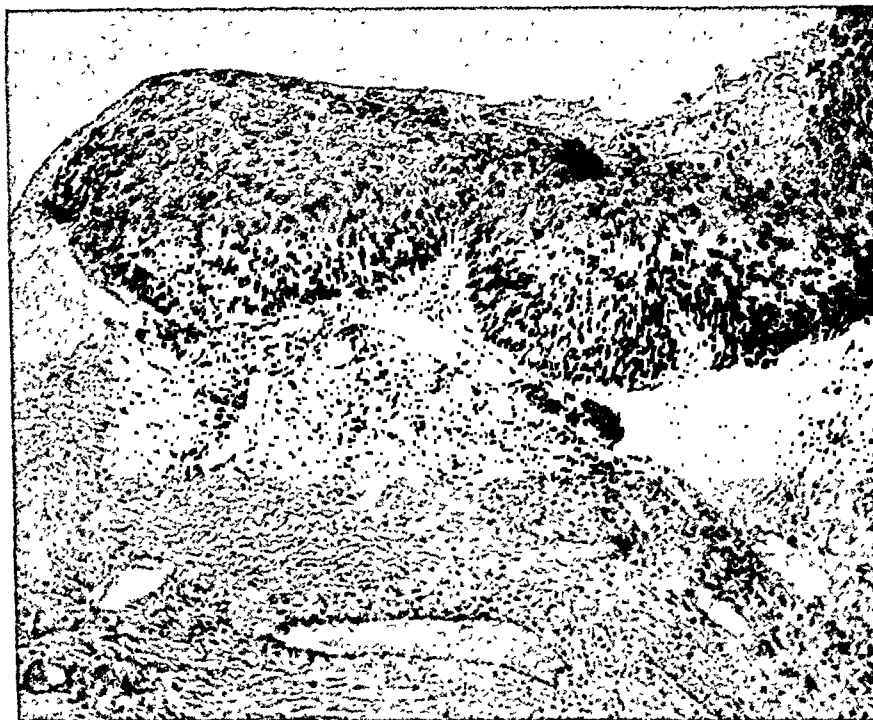


Fig. 1.—Path. No. 56452. Typical intraepithelial carcinoma.

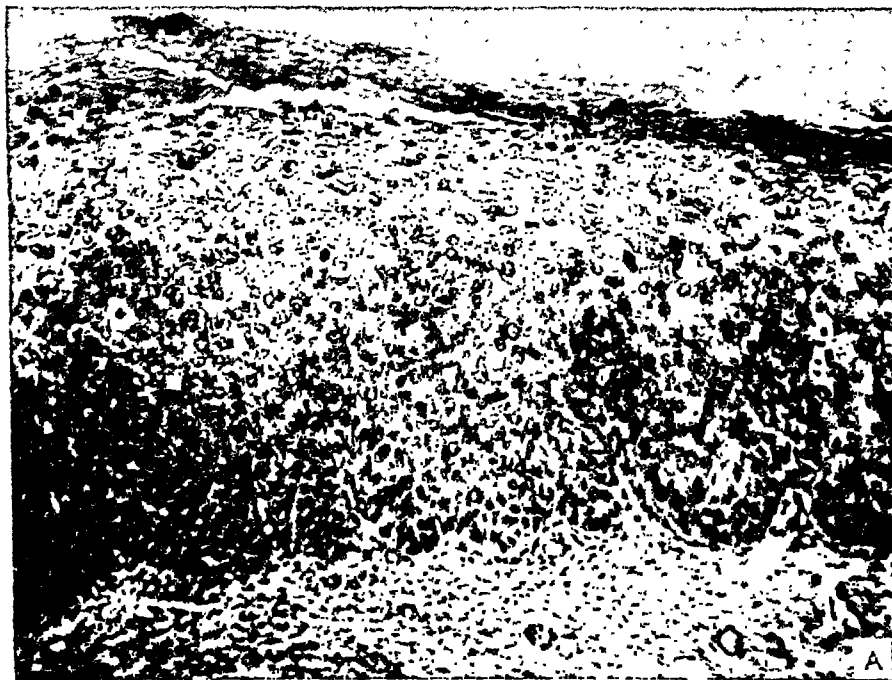


Fig. 2.—Path. No. 59392. Typical carcinoma in situ.

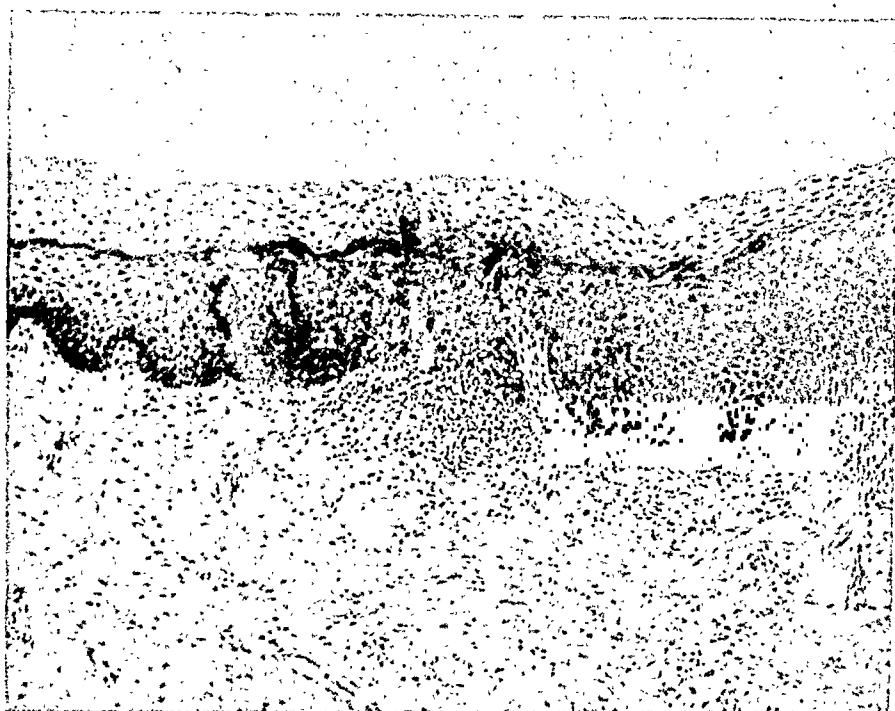


Fig. 3.—Path. No. 54078. Oblique line of demarcation between abnormal and normal epithelium.

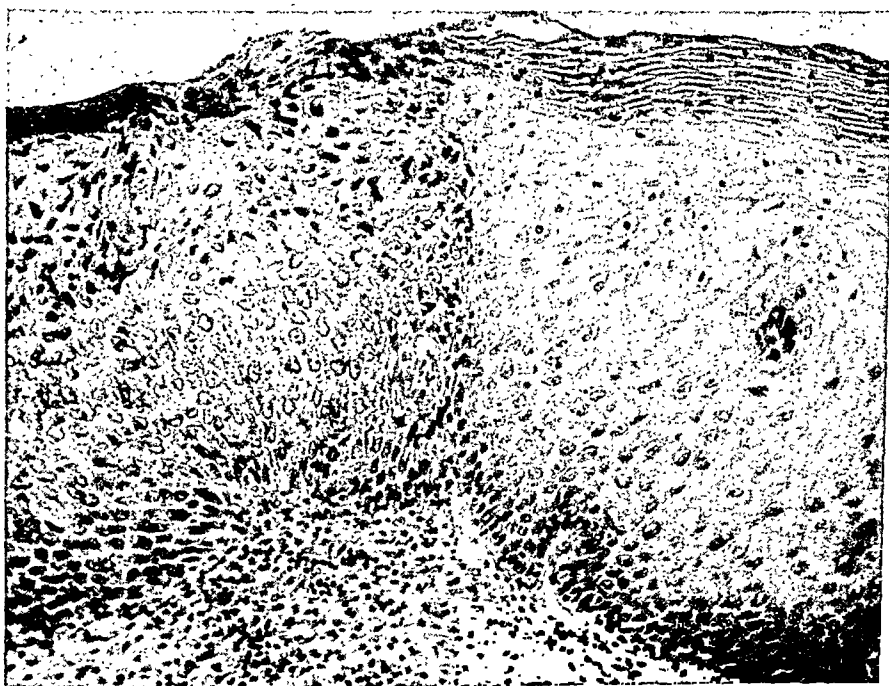


Fig. 4.—Path. No. 75417. Demonstrating an abrupt perpendicular change between abnormal and normal epithelium.

specimens changes in the basal portion of the surface epithelium which we interpret as basal-cell hyperactivity and for want of a better name we have designated these changes as such (Fig. 5). There appears to be an active proliferation of the dark hematoxylin-stained basal cells. These cells possess hyperchromatic nuclei and a varying number of mitotic figures. In the removed cervixes we have frequently seen this activity of the basal cells adjacent to typical intraepithelial carcinoma and invasive cancer. All gradations of basal-cell hyperactivity are seen until the entire thickness of the epithelium is taken

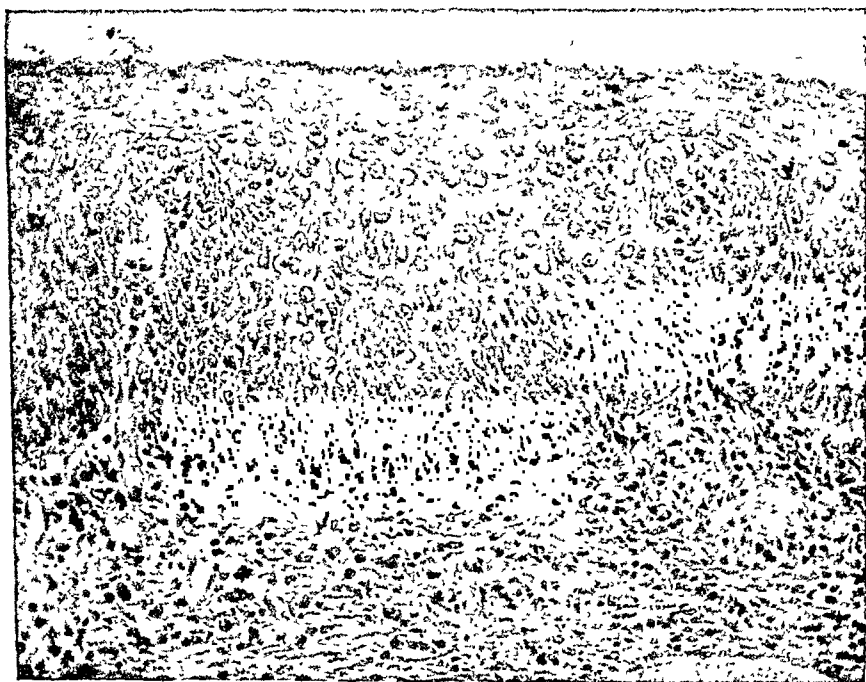


Fig. 5.—Path. No. 72800 . Basal-cell hyperactivity.

over by it, when the picture becomes identical to carcinoma in situ. As this hyperactive basal epithelium pushes upward, it may be sharply demarcated from the normal epithelium above or, more commonly, the abnormal and normal epithelium may blend gradually. We have observed basal-cell hyperactivity blend into full blown intraepithelial cancer so frequently, histologically, that we have become deeply concerned about its significance. The unanswered questions which have arisen in our minds are:

Does intraepithelial cervical cancer always begin as basal-cell hyperactivity?

Does basal-cell hyperactivity always progress into intraepithelial cancer?

May basal-cell hyperactivity remain constant indefinitely or may it sometimes regress?

Histologically, there is a strong suggestion that basal hyperactivity does on occasion mature into carcinoma in situ but it cannot be stated with certainty that this occurs. The following case illustrates the possible progression:

The first biopsy was taken on Jan. 8, 1947, and showed only basal-cell hyperactivity (Fig. 6, A). A second biopsy was taken on Jan. 20, 1947, and again showed basal-cell hyperactivity (Fig. 6, B). A third biopsy, taken on Oct. 9, 1947, showed full blown intraepithelial cancer and on the basis of this finding a panhysterectomy was done (Fig. 6, C). When the cervix was sectioned, invasive cancer was finally found (Fig. 6, D).

On the other hand, on several occasions we have biopsied cervixes and found definite basal-cell hyperactivity and repeated biopsies over months of time have shown only further basal-cell hyperactivity or no abnormality at all.

From a practical point of view we have regarded basal-cell hyperactivity as a warning, calling for repeated biopsies until such time as one can be convinced histologically that carcinoma does or does not exist. It is in these cases that we have often resorted to a cervical conization, done with a scalpel and followed by an electrosurgical conization to control bleeding. The cone of tissue is cut into several blocks and sectioned. By this procedure one can usually feel quite certain in establishing or ruling out carcinoma.

Whatever the final answer may be concerning the relationship of basal-cell hyperactivity to carcinoma in situ, the more practical problem today concerns itself with the relation of intraepithelial cancer to invasive cancer. Since the beginning of our study in 1940, we have diagnosed carcinoma in situ from biopsy 75 times. In some of these biopsies suggestive or slight invasion of the subepithelial tissues was noted but in all instances the changes in the surface epithelium were typical of carcinoma in situ. In 67 instances, we have performed a modified Wertheim operation for this condition. In one instance, the lesion was discovered in a cervix amputated in the course of a Manchester operation. In the remaining seven cases, conization of the cervix was done before radium was applied. Hence, in a total of 75 cases we have had the entire cervix or a generous cone for complete sectioning. In 55 instances, we found microscopic invasion. It is extremely difficult to put into descriptive terms one's criteria for invasion. We have, therefore, pictured here sections of several typical biopsies showing carcinoma in situ and sections of the corresponding cervixes showing what we consider to be invasive cancer (Figs. 7 and 8). In ten cases in which the biopsy showed carcinoma in situ, only carcinoma in situ was found in the removed cervix and in ten instances no abnormality was found in the removed cervix, the entire lesion having possibly been removed at biopsy.

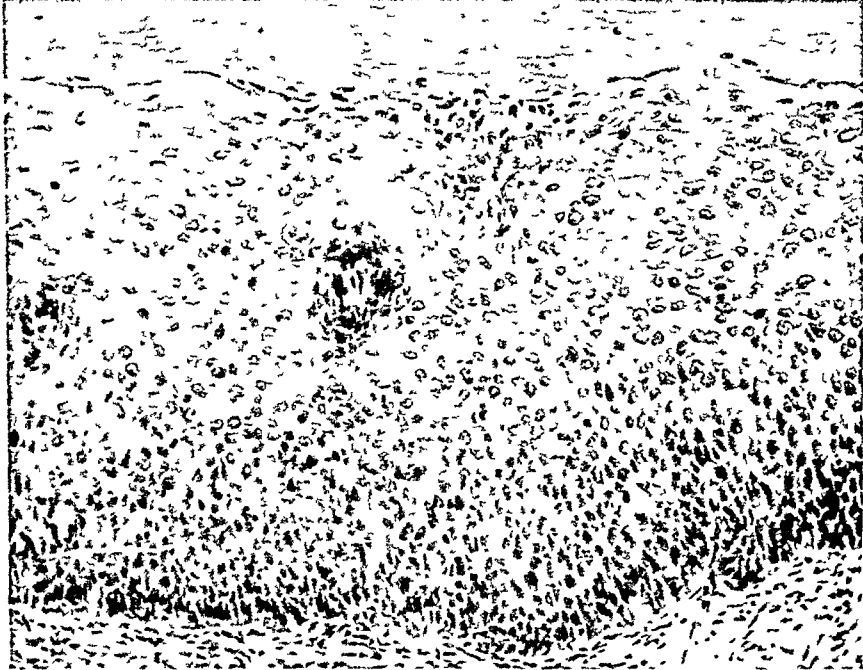
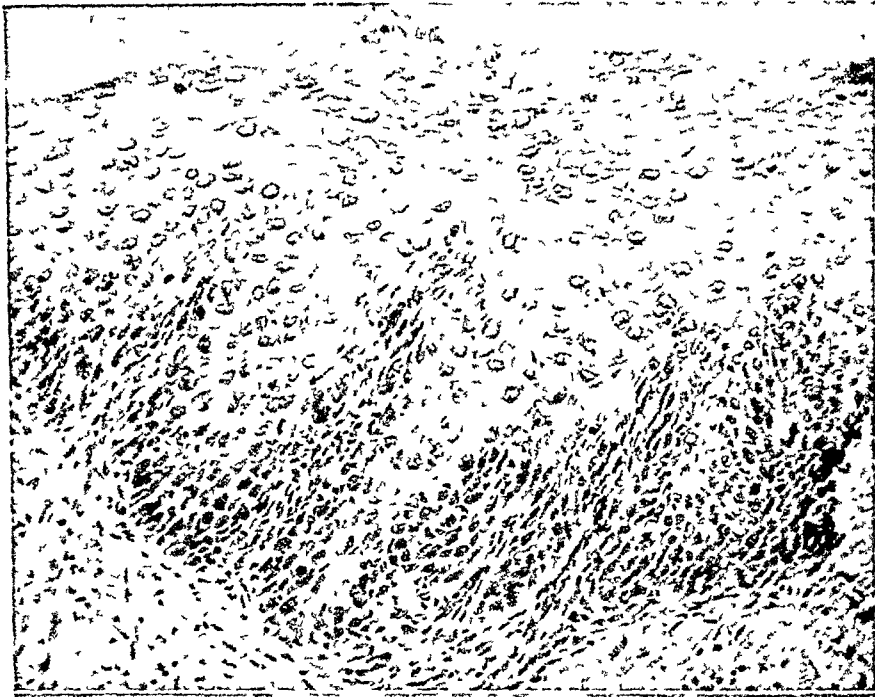
In order to study further the relation between carcinoma in situ and invasive cancer, we have made sections through the entire lips of several cervixes. These sections are pictured in low power in Figs. 9 to 11. High power magnification of selected portions of these sections show typical surface cancer and the plugs of invasive cancer lying well beneath the surface. It is noteworthy that the plugs of invasive cancer in these sections are found at a considerable distance from the rather extensive surface cancer in situ.

From these studies it would thus appear that carcinoma in situ or intraepithelial carcinoma should be considered strictly as a histologic diagnosis and be regarded as indicating one of three clinical possibilities:

1. That the biopsy has been taken from the periphery of an advanced cervical cancer as was originally described by Schottländer and Kermauner.
2. That microscopic invasive cancer is present elsewhere in the cervix as was the case in 55 of our 75 cases.
3. That only carcinoma in situ is present and no invasion has as yet taken place. This was found to be the case in 20 of the 75 cases which we studied.

Therefore, in evaluating each case clinically the gross appearance and feel of the cervix should be considered. If, for example, a biopsy shows only carcinoma in situ but the gross appearance of the cervix is suspicious of more advanced cancer, more biopsies or, in some instances, a sharp conization should be done to evaluate the extent of the entire lesion. This, we believe, is of particular importance because of our views on treatment which will be discussed later in this paper.

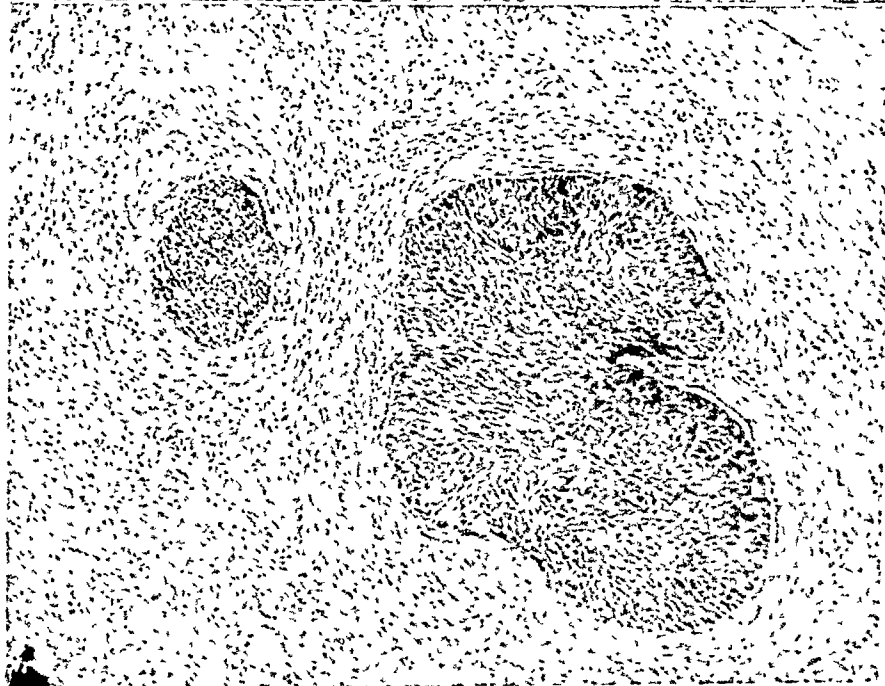
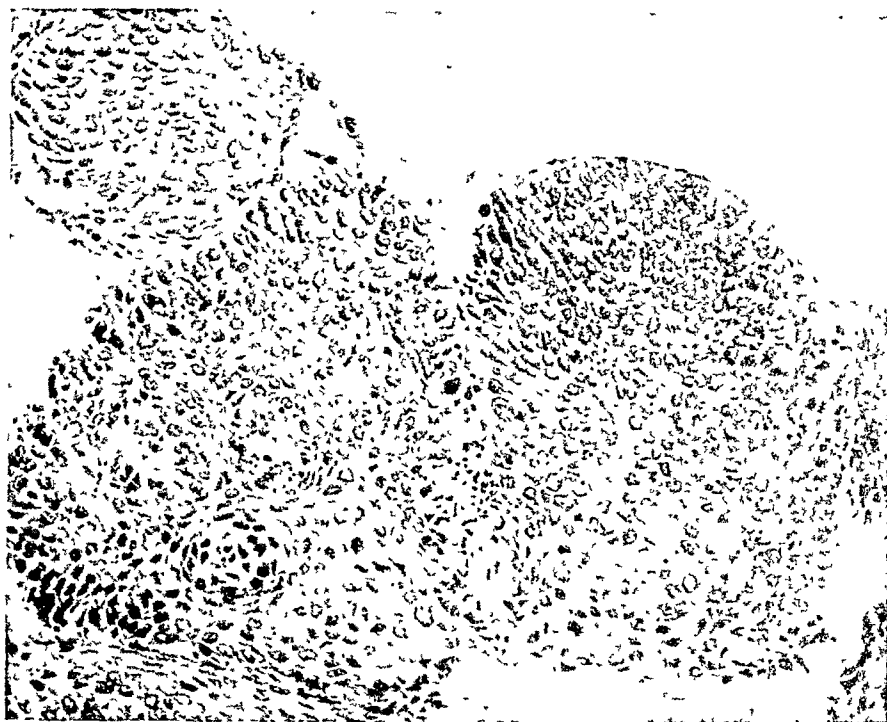
A.



B.

Fig. 6.—A, Path. No. 68601. Biopsy taken Jan. 8, 1947, showing only basal-cell hyperactivity. B, Path. No. 68877. Second biopsy taken Jan. 20, 1947, again showing only basal-cell hyperactivity.

C.



D.

Fig. 6.—C, Path. No. 72865. . Third biopsy taken Oct. 9, 1917, showing intracervical cancer.
D, Path. No. 73165. Showing plug of carcinoma in the depth of the removed cervix.

In formulating our concept concerning the relation of carcinoma in situ to invasive cervical cancer, a survey of the more important reports in the literature should prove valuable. It is well known that the curability rate has been high with various types of therapy. For the moment, we are not concerned



Fig. 7.—A, Path. No. 74370. Biopsy showing only intraepithelial cancer. B, Path. No. 74454. Section of removed cervix showing invasive cancer.

with that but rather with the ultimate fate of those patients who were not treated or who failed to be cured in spite of treatment. It is this group which will cast most light on the question of malignancy of these lesions.

Schiller⁵ has reported one recurrence after five years and two recurrences before the lapse of five years following hysterectomy.

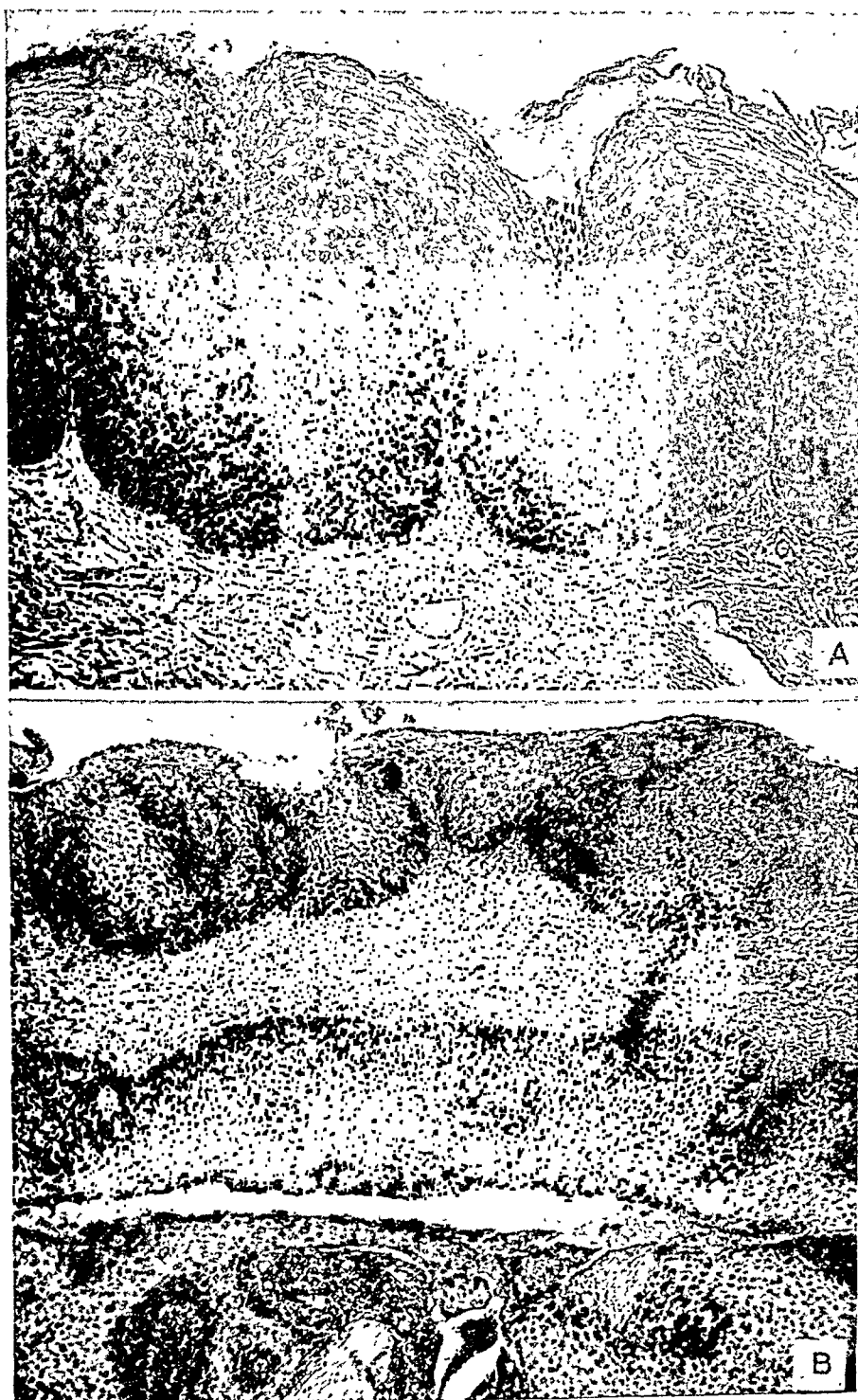


Fig. 8.—A, Biopsy showing carcinoma in situ. B, Path. No. 54078. Section showing intra-epithelial cancer and invasive cancer in removed cervix.



Fig. 9.—Path. No. 62339. *A*, Low-power section of entire lip, showing normal surface epithelium, carcinoma in situ, and invasive cancer. *B*, Medium magnification, showing invasive area. *C*, High power, demonstrating cellular changes.

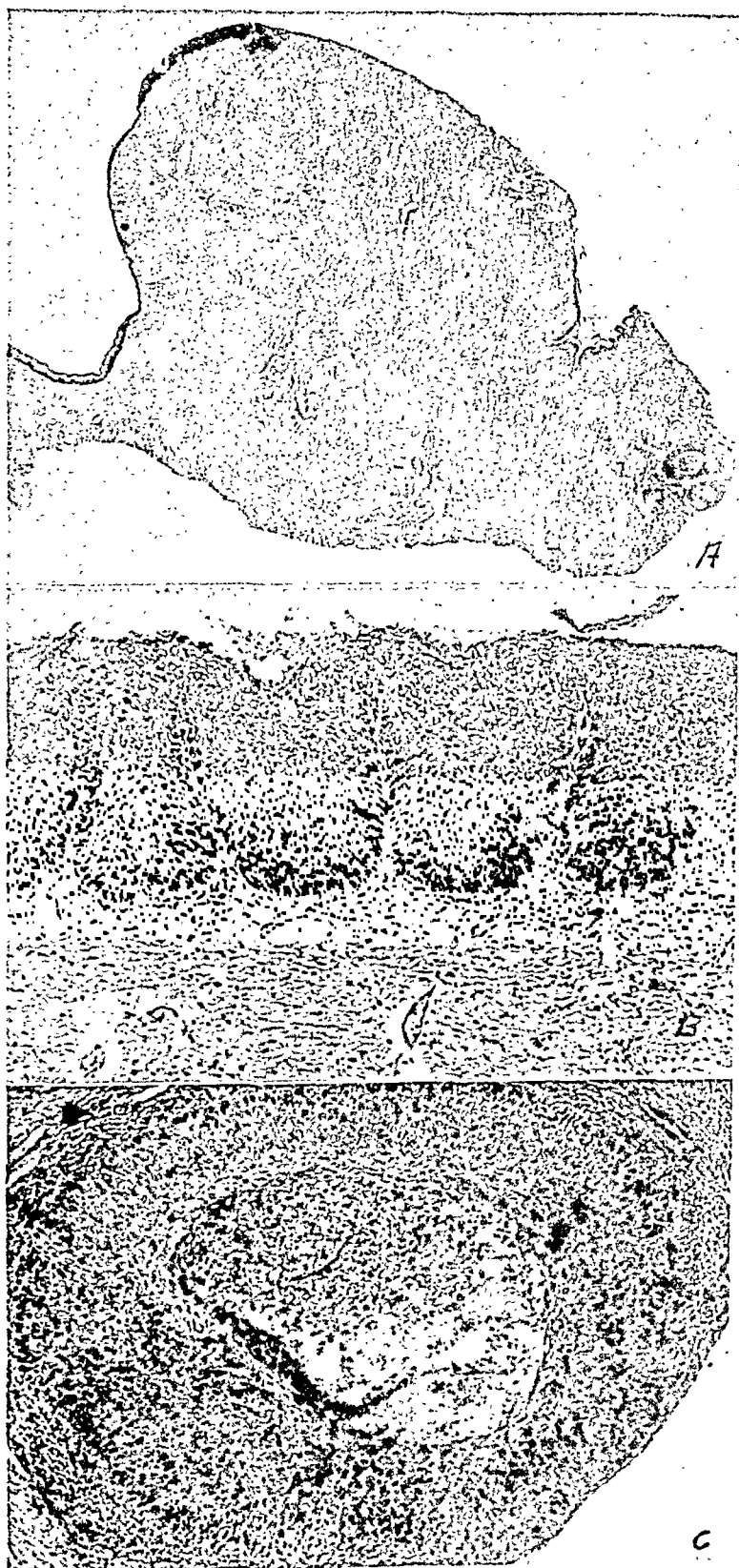


Fig. 10.—Path. No. 65809. A. Low-power section of entire cervix. B. Surface epithelial changes, higher power. C. High power of plug of invasive cancer. Note distance of this plug from surface cancer.

Stevenson and Scipiades⁶ reported one case in which carcinoma in situ was present in a bit of tissue removed at trachelorrhaphy. This was not recognized in 1919. Two years later the cervix appeared normal on speculum examination. Nine years after the trachelorrhaphy the patient presented herself with an advanced cauliflower-like cancer of the cervix. A second case reported by them was that of a woman on whom a biopsy showed typical intraepithelial carcinoma. She died of another cause three and a half years later. Although she had never had any symptoms of cervical cancer, the sectioned cervix was riddled with invasive cancer.

Pund et al.⁷ have recorded an untreated case in which advanced carcinoma was found four years and nine months after the initial biopsy, which showed only carcinoma in situ.

Smith and Pemberton⁸ reported four cases in which tissue removed by biopsy or trachelorrhaphy showed intraepithelial cancer and in which clinical carcinoma was discovered four years and nine months, six years and one month, twelve years and six months and four years and one month, respectively, afterward.

Schmitz and Benjamin⁹ reported one untreated case in which invasive cancer was found nine months after the in situ lesion was discovered.

Knight¹⁰ reported one case which ended fatally three years after treatment by irradiation. Another of his cases was found to have invasive cancer four years and eleven months later.

Younge¹¹ reported invasive cancer developing in two cervices two years and two months and three years and four months, respectively, after biopsy.

Taylor and Guyer¹² reported one untreated case in a patient in which clinical cancer appeared seven years after the proved existence of carcinoma in situ.

One of our patients on whom only irradiation therapy was used died six months after the discovery of the in situ lesion. The autopsy showed metastatic cancer.

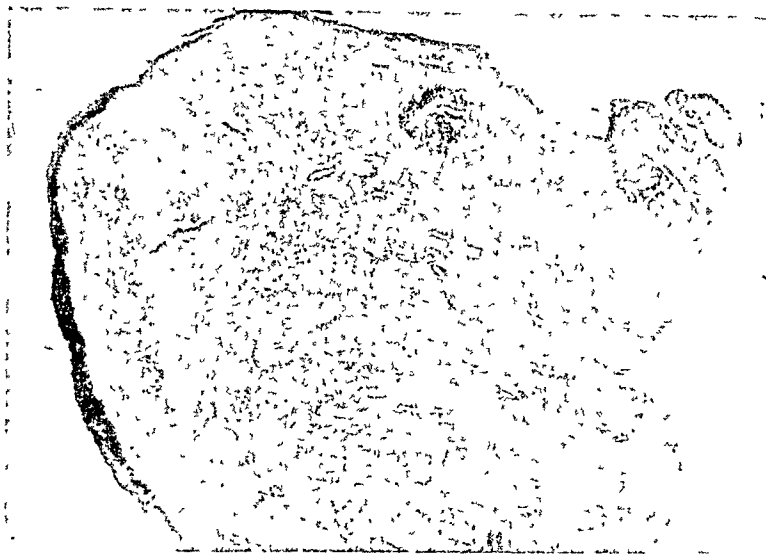
We have cited these cases somewhat repetitiously in an attempt to bring forth authentic clinical evidence to show that in at least 17 cases clinical cancer has followed pre-existent intraepithelial cancer. It is evident that clinical cancer may not make its appearance for many years after the known existence of the surface lesion. On the other hand, our own case terminated fatally after only six months. Such rapid progress is probably exceptional.

The age of these patients as compared with that of clinical cancer confirms our belief that the surface lesion may be relatively dormant for years before blossoming forth as clinical cancer. The average age of our 75 women with cancer in situ was 37.1 years, the youngest being 24 and the oldest 53 years, in contrast to the average age of 48 of women with clinical gross cervical cancer. Pund et al.¹³ found the average age of his in situ group to be 36.6 years. Further evidence of the possible long duration of the noninvasive lesions is offered by Knight, who reported a case in which a preinvasive lesion was found in an amputated cervix. The neoplasm was found to be still present in the remainder of the cervix five years later.

Whether all carcinomas in situ are destined to develop into clinical carcinoma cannot be stated. It is probable that many women harboring the condition die of other causes before the lesion develops to the stage where it becomes clinically apparent. However, the microscopic and clinical evidence is such that it is our belief that they should not be considered "precancerous" lesions but rather an early stage of true cancer.

From the standpoint of reducing the mortality from cervical cancer, this lesion assumes great proportions. Here is a lesion, virtually on the surface of the body, detectable by biopsy, which in many instances gives us years of warn-

A.



B.



C.

Fig. 11.—Path. No. 54078. A. Low power of entire cervical lip, showing extensive carcinoma in situ and areas of invasive cancer. B. High power of surface epithelium. C. High power of invasive area.

ing before it becomes a lethal lesion. In at least seven of the cases which eventually showed invasive cancer, the cervix appeared normal in all respects and the biopsies were made purely routinely in our study of cervixes in women who were to have hysterectomies for benign lesions, such as myomata. In none of the patients of this series did the cervix present the clinical picture of cancer. The majority, however, did present some abnormal appearance and were diagnosed clinically as cervicitis, erosion, eversion, laceration, and leucoplakia. Since we have found almost all of these early lesions arising in the stratified squamous

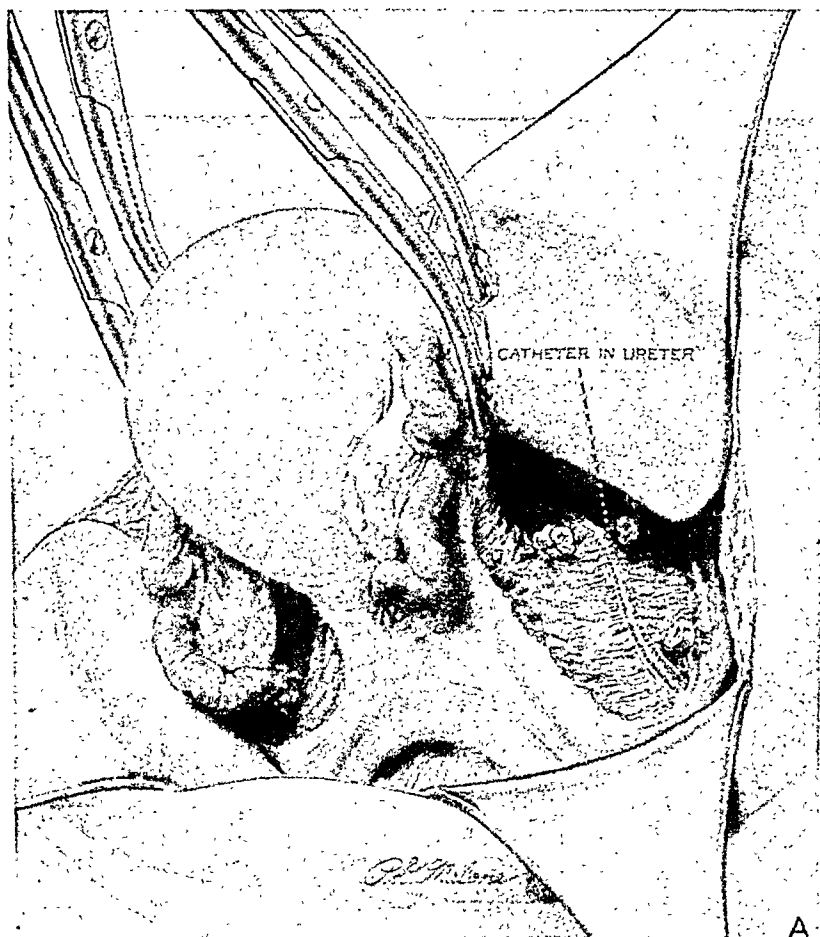


Fig. 12, A-D.—Modified Wertheim operation.

A. Broad ligament has been opened widely, exposing ureter which has been catheterized. Uterine vessels have been ligated at some distance from the uterus.

epithelium at its junction with the columnar epithelium, we have a guide as to where to take our biopsies when no local lesion is visible. The sharp demarcation between the pink squamous epithelium and the deep red columnar epithelial surface is usually clearly visible. Occasionally this junction is within the cervical canal, a point not to be forgotten in taking biopsy specimens.

With the use of the ordinary punch biopsy forceps, troublesome bleeding is rare. Recently, we have routinely inserted a Tampax after taking the biopsy and instructed the patient to withdraw it on the following day. Occasionally we have touched the biopsy site with the cautery to stop an active ooze.

We are omitting any comments concerning the diagnosis of carcinoma in situ by cytologic methods. At the present time we do not have sufficient data on this phase to justify any conclusions and we know of no other workers who have enough data to be significant.

From the standpoint of symptomatology, little is to be said concerning this group of cases except to emphasize that often these lesions are completely asymptomatic; but of equal importance is the fact that 58 per cent of these women had some type of irregular vaginal bleeding. Of these, however, this symptom was the presenting complaint in only a few. In the majority it was elicited only through a careful and complete investigation of the history. We were impressed with the fact that in many of the cases in which abnormal bleeding was present it took the form of postcoital spotting. The majority of these lesions were discovered by routine investigation of patients who presented themselves with common gynecologic complaints such as leucorrhea, backache, sterility, dysmenorrhea, and abdominal pain.

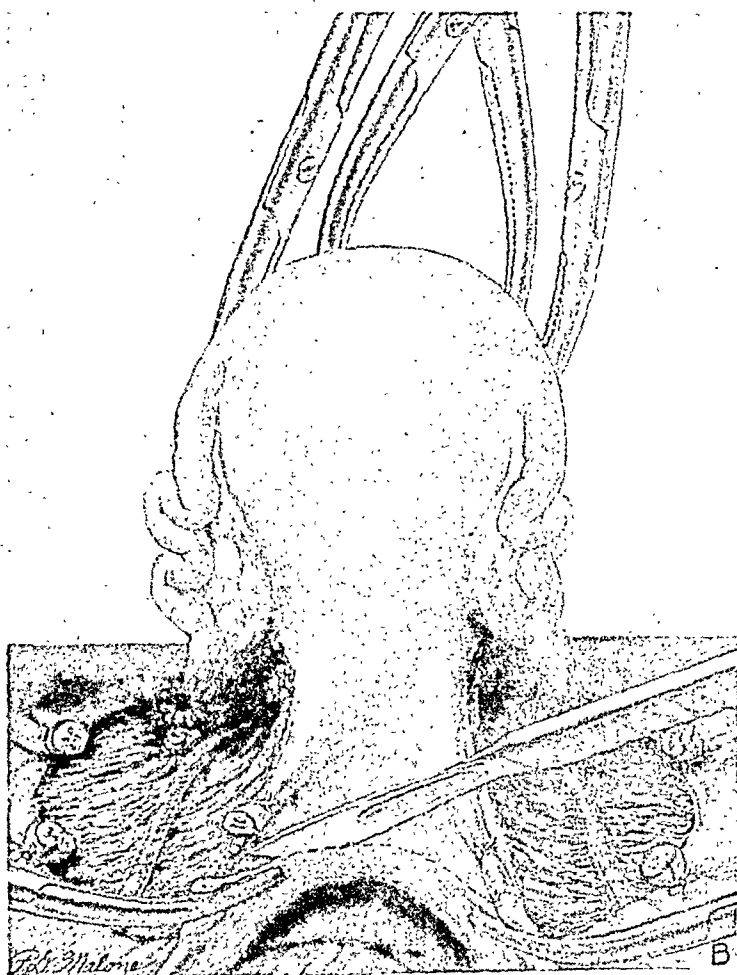


Fig. 12, B.—Uterosacral ligaments severed.

The question of the treatment of carcinoma of the cervix, after having been settled for many years in favor of irradiation, has been opened again by the clinical experiments which are at present being undertaken with the Wertheim operation on selected cases falling into Stage I and early Stage II (League of Nations). It is not the purpose of this paper to enter the controversy concerning surgery versus irradiation in the treatment of gross cervical cancer. It is our belief that the above-described microscopic lesions should be considered in a special category from the standpoint of therapy. We regard them as a subgroup of Stage I and the results of their treatment should be reported separately to avoid confusion with existing reports on Stage I.

We originally operated on these patients with the purpose of obtaining the entire cervix for microscopic study. From a study of these cervixes it is obvious that one cannot be confident of a cure from cervical amputation. We have three cases in our series in which plugs of carcinomatous tissue were found well up in the cervical canal. The operation which we have performed 67 times is a modification of the Wertheim procedure (Fig. 12). The gland dissection is omitted, but the parametrium is removed for about two cm. on each side of the cervix. A fairly wide cuff of the vagina is removed with the cervix because we have frequently observed a widespread involvement of the surface by the intraepithelial growth, even when its appearance was normal. The pubocervical fascia is not stripped from the vagina as is our custom in performing total hysterectomy for benign disease (Fig. 12, C).

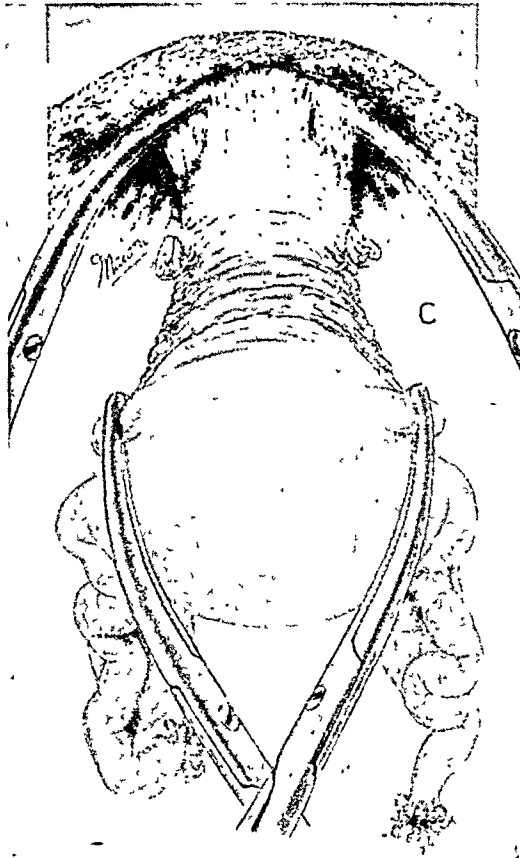


Fig. 12, C.—Pubovesico-cervical fascia is left attached to vagina and clamped with it before amputation.

Preoperative ureteral catheterization is a great convenience and safeguard. It is recognized that the ureters can usually be isolated readily without catheterization but at times considerable dissection is necessary, particularly on fat individuals. Bleeding may ensue and stripping the ureter of its blood supply may result in fistula. With catheters in the ureters, the operator can travel down the parametrial regions rapidly and safely by simply palpating the catheter before placing each clamp. We have had no ureteral fistulas in our series. The vagina may be closed or drained, depending on the preference of the operator (Fig. 12, D). We have observed no advantage in drainage.

Since many of these lesions occur in young women and since the ovary is a place of late metastasis of cervical cancer, we have saved an ovary in some of the younger women. The theoretical objection to this might be advanced on the basis of preservation of the source of estrogen in the presence of malignancy. Although estrogen is the growth hormone of the sex organs, there is no real clinical evidence to indicate that it is a factor in the production of cervical cancer. Our results have vindicated our decision to obviate bilateral oophorectomy in the younger women. Our results to date also justify our decision to forego lymphadenectomy in these microscopic lesions.

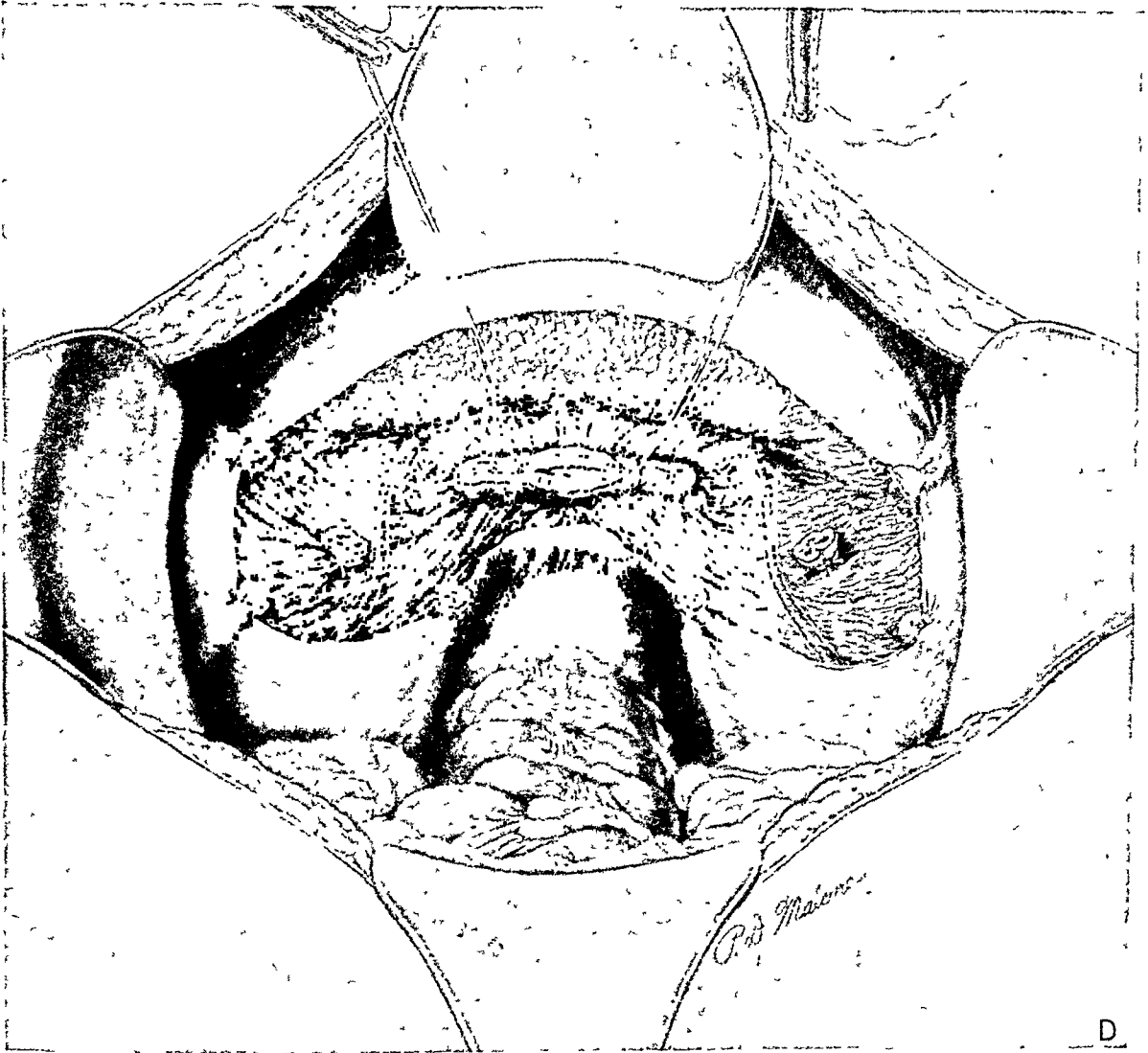


Fig. 12, D.—Vagina being closed before its suspension and peritonealization.

All of our 67 cases operated upon between Jan. 1, 1940, and Jan. 1, 1948, are living and without recurrence. Although we realize that sufficient time has not elapsed to attach much statistical significance to these results, we are much encouraged by them and have seen no reason to change our therapeutic attack. Our only death occurred in one of the seven cases in which irradiation therapy was used.

Finally, we wish to emphasize that this study has no bearing upon the present-day controversy of the Wertheim operation versus irradiation in gross cervical cancer. We regard these cases as a special group and we have treated them in a special manner. We would, indeed, be greatly distressed to have the above results used in support of the operative treatment of gross cervical carcinoma. It would be particularly regrettable if the impression were obtained that gross cervical cancer should be treated by an operation in which gland dissection is omitted.

The authors wish to express their appreciation to Miss Eva Hildebrandt, chief tissue technician, for her great industry in cutting thousands of sections, without which this study could not have been made.

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Discussion

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Once more Dr. TeLinde, with the able cooperation of Dr. Galvin and their associated workers, has presented further evidence of continued and meticulous histologic and clinical observation concerning noninvasive cervical carcinoma in which actual invasion was discovered subsequently.

This present action clarifies to a fine degree the criteria set forth with regard to the diagnosis of carcinoma in situ. It is one thing, however, to declare these criteria and another to interpret them properly. What to one pathologist might appear to be a variation in cellular structure and sufficient to be called carcinoma, might to another represent only hyperplasia. This is not true of the author's report, for they have shown how one must be extremely careful not to confuse a tangential section with a focal proliferation of the cells, a difficulty that may be encountered by even the most experienced tissue worker.

As is the case with the skin, the bronchus, and elsewhere, it is probably true that carcinoma begins in the basal cells. Whether or not basal-cell hyperactivity is always a precursor of carcinoma is controversial, as the authors have been frank to admit. Regardless of this conflict of opinion, however, there seems to be little doubt of the author's correct viewpoint on the existence of intraepithelial cancer as revealed by these very complete studies and follow-up observations on 75 patients with cervical carcinoma in situ seen since 1940. In fact, I would now go a step further than they and refer to such lesions simply as "carcinoma" rather than speak of them as "an early stage of true cancer"—and this implies implicit confidence in their research.

It is desirable to emphasize again that a long interval of time may elapse between recognition of carcinoma in situ and the development of a truly invasive lesion, for such occurrences are sometimes observed in carcinoma elsewhere, as for instance on the face. The authors have cited references to such instances but an explanation of these vagaries is still to be found. In this connection I would like to place on record the case of a patient whose cervical tissue in 1924 showed what we would now consider carcinoma in situ, but in whom no further treatment was instituted at that time because of laxity in truly evaluating the

abnormality. Nine years later, in 1933, without interval observation, the patient appeared with a Stage III carcinomatous lesion of the cervix. This somewhat parallels the case of Stevenson and Scipiades cited by the authors.

At Jefferson Hospital we have been endeavoring to carry out a study of this character, but to date have no comparable series to report upon. To some extent this has been due to the conservative attitude previously taken by us with respect to demanding actual invasion as the criteria of malignancy. We do have at present, however, six patients under observation for several years in whom primary cervical biopsy could be considered as representing carcinoma in situ, and in all of whom subsequent endocervical resections of some magnitude revealed nothing even to suggest further existence of an intraepithelial lesion. This might be interpreted as indicating elimination of the cancer by the initial biopsy, but, in any event, no further treatment has been given these patients—and this for the sole purpose of trying to learn more about the situation by simply observing these patients at regular intervals for a continuing long period of time.

For the past year or more we have chosen to deal with any cervix showing abnormality, whether local symptoms are present or not, by a circular scalpel biopsy to include the squamous-columnar line of demarcation, following this by endothermic resection using the loop. We prefer this technique to punch or multiple biopsy methods. Certainly the pathologist prefers ample, uncharred sections of tissue. To date, in several hundred routine cervixes serially studied in this manner, no carcinoma in situ has been reported.

The authors have purposely omitted reference to the diagnosis of carcinoma by cytologic methods. It might interest them to know that in the cancer detection clinics of Philadelphia, conducted under the auspices of the Donner Foundation in conjunction with the Philadelphia County Medical Society, my departmental associate, Dr. A. E. Rakoff, has studied 5,000 vaginal smears cytologically. Of six positive smears found, only one was from a patient in whom the signs and symptoms did not actually suggest cervical carcinoma. This is important from the point of view of a screening program, for a single negative report means only that. On the other hand, the Boston group (Hertig, Fremont-Smith, Graham and Meigs) have reported a relatively high number of positive smears in preinvasive carcinoma that compare to better advantage than initial biopsy in one series mentioned.

One word as to treatment. It would appear that, if we accept the concept of malignancy without reservation, then therapy should be in full measure, whether by irradiation or by surgery. The authors, however, have shown in their follow-up that their method of surgical management has to date been adequate with respect to survival.

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—The epithelial changes characteristic of noninvasive carcinoma, or carcinoma in situ, have been recognized and talked about by dermatologists for many years. As is well known, they are seen in such skin conditions as Bowen's dermatosis, senile and arsenic keratoses, and in leucoplakia.

Extensive study of such changes in the epithelium of the cervix uteri, in which the author of this paper has taken an active part for a long time, is of more recent date. Previously, these lesions were thought to be exceedingly rare in any mucous membrane surface epithelium.

His emphasis, now, through additional experience, on activity, or proliferation of cells in the basal layer of the epithelium puts us a step closer in cervical histopathology to the dermatologist and his experience with basal-cell carcinoma—a lesion usually of sluggish growth and benign nature, but which may become dangerous at any time.

Quite properly the author points out that whatever their form, these epithelial changes occur commonly at or near the margin of invasive carcinoma and very rarely as solitary isolated alterations. Such a fact makes debatable the method of treatment. Isolated epithelial lesions of this type are undoubtedly cured by conization or amputation of the cervix, but who has the courage to stop there when it is never known what the remainder of the cervix may contain?

The logical danger to be seen in Dr. TeLinde's handling of these patients is that his treatment is also less than adequate surgical treatment for actual carcinoma of the cervix,

though quite adequate probably for 20 of his 75 patients. The remainder of his patients have small, but not necessarily early, carcinomas and before any opinion is formed whatsoever, we must await his report of five-year survivals.

As a general teaching concept, it would seem that emphasis on carcinoma in situ with conservative operation has stirred up interest in the study of cervical epithelium, but it has also contributed to the present furor for return to surgical treatment of carcinoma of the cervix in an unhealthy manner. In the first place, the mere mention of "carcinoma in situ" is beginning to provide in some quarters an excuse for operation—whether such a lesion actually exists, as it does rarely, or turns out to be, as is more common, the margin of an invasive cancer. Psychologically, with a laboratory report of carcinoma in situ, the pathologist is *allowed* to share the responsibility for later treatment failure. It is human nature, too, to welcome the return of an operation which anybody can perform, but which admittedly is inadequate for cure of cancer. It would seem that in this combination of circumstances may eventually lie elements of trouble and danger, if acceptance becomes widespread.

DR. THOMAS C. PEIGHTAL, New York City.—Since 1944, when Dr. TeLinde reported that 15 out of 16 carcinomas in situ also showed evidence of invasion, he has now collected a total of 75 cases in which this diagnosis of intraepithelial cancer has been histologically identified from biopsies.

During the collection of this data he has been impressed with the importance of basal-cell hyperactivity which has been seen to occur alone, in conjunction with carcinoma in situ, and surrounding frank invasive cancer of the cervix. He asks us to help him answer three questions concerning basal-cell hyperactivity, most pertinent of which is, "Does basal-cell hyperactivity precede carcinoma in situ?" Or, to put it another way, "Is basal-cell hyperactivity just a pathologic step earlier than intraepithelial cancer?"

Leucoplakia, so-called, may proceed to a degenerative benign type of lesion, or it may undergo basal-cell hyperactivity, often with keratinization of the upper layers. Basal-cell hyperactivity is often seen in the same section with carcinoma in situ.

It is only through such reports as Dr. TeLinde's, which may come from many other clinics, that this important question can be answered. We feel that basal-cell hyperactivity in biopsy material is a grave warning—not to be regarded lightly—and that its presence calls for repeated biopsy at frequent intervals. We agree with Dr. TeLinde that this basal-cell hyperactivity had best be considered as precancerous until proved otherwise.

²As regards carcinoma in situ, Dr. TeLinde has shown that 73.3 per cent of his cases had, at the time of biopsy, frank invasive cancer within the cervix (55 out of 75 cases). For this reason we agree too that carcinoma in situ is no longer to be regarded as merely precancerous but as true cancer and, therefore, in all instances, must be treated as if it were frank invasive cancer.

We use the Schiller test as an aid in obtaining biopsies and emphasize that the examiner must be alert to the slightest abnormal epithelial changes. The historian too must be careful in eliciting symptoms for, as Dr. TeLinde states, "While many of these women are asymptomatic," at least 58 per cent of his cases had some type of irregular bleeding—most often postcoital spotting.

Dr. TeLinde lists 17 cases of carcinoma in situ from other sources which ultimately went on to invasive cancer in from three to nine years. To this list we would add another case.

Dr. TeLinde, where possible, treated his cases by modified Wertheim procedure (67 of the 75 cases were so treated), in no instances removed the retroperitoneal lymph nodes, and in a few young women even left in the ovaries.

This is the only part of his paper to which we cannot wholeheartedly agree. In the first place, we feel one cannot know how often nodes may be involved even in carcinoma in situ cases unless one dissects out these nodes in a goodly number of cases. Again, since 73 per cent of his carcinoma in situ cases really had invasive cancer, it is more than likely that some of these women had positive nodes already at the time of his modified Wertheim procedure. We shall be interested to know what his follow-up on these 67 cases will show in the next few years. Either his omission of node dissection will be justified or his percentage

of recurrence will make him remove the nodes in the future. Time will tell but we urge that in a sufficient number of instances node dissection be carried out to establish the incidence of their involvement in these early lesions.

Dr. TeLinde quotes Schiller as reporting at least three recurrences in five years or less after hysterectomy in such cases.

We would emphasize that trachelectomy alone as a treatment for carcinoma in situ is definitely inadequate. Time alone will tell whether he is justified in preserving ovaries in the younger women.

There are some among us who, I am sure, will not agree that surgery is the best method of treatment for these early cases; and will maintain that this is one group at least in which radium and x-ray may well produce their best results. As Dr. TeLinde pointed out, "This study has no bearing on the present-day controversy of the Wertheim operation versus irradiation in gross cervical cancer. This is a special group which should be treated by surgery if you like, by radium if you prefer that method; but let us keep them segregated and in reporting the results through the years let time alone assess our efforts."

Dr. TeLinde's work has greatly increased the sum total of our knowledge concerning precancerous and early cancerous changes in the cervical epithelium. He has given us the stimulus to be on the lookout for these changes, has taught us how to identify them, and how best to treat them. He, more than anyone else, has kept our specialty abreast clinically and pathologically with the trend of the times—namely, early cancer detection—and has given us the ability to evaluate competently the cervical epithelial changes in the increasing multitude of women that our national cancer drive is daily sending to us for examination.

DR. E. D. PLASS, Iowa City, Iowa.—Some work my colleagues, O. F. Kraushaar, J. T. Bradbury, and W. E. Brown, have done in the past two years seems pertinent to this discussion. Using the Papanicolaou method, they have screened 5,314 women for genital cancer. Among the group of "positive" smears obtained were 14 from women who gave no histories of pelvic abnormalities, and in whom careful digital and visual examinations of the genital tract provided no suspicion of a malignant lesion. Biopsies taken on the basis of the "positive" cytologic abnormalities showed definite evidence of cancer, in five instances the lesion was definitely invasive but in the other nine the diagnosis of "carcinoma in situ" was made with the knowledge that more sections might well have revealed invasion.

Illustrative cases include B. P., aged 64 years, who was treated in the medical department in 1946 for diabetes mellitus. In May, 1947, after admission for a medical check-up, pelvic examination was negative. In December, 1947, diarrhea led to another admission. Pelvic examination was again negative, but the routine vaginal smear showed abnormal cells. Biopsy revealed early invasive carcinoma of the cervix. Treatment was with 4,950 mg. hr. of radium.

G. H., aged 58 years, had had a subtotal hysterectomy in 1934. Five years later, posterior gastroenterostomy was done for duodenal ulcer with pyloric stenosis. On this admission, pyelonephritis with possible uremia was also diagnosed. In 1943, jejunojejunostomy was performed for subacute obstruction. In March, 1948, she was admitted with pyelonephritis. Routine vaginal smear was "positive." Pelvic examination showed an "atrophic cervix." The patient died in uremia and the cervix was obtained at necropsy. Serial sections revealed a "carcinoma in situ."

L. B., aged 30 years, was admitted in March, 1948, because of mild cystitis and trigonitis. Routine vaginal smear showed abnormal cells. Pelvic examination was negative. Cervical biopsy revealed "carcinoma in situ." Total hysterectomy and right salpingo-oophorectomy were done. No neoplasm could be found in the remaining cervical tissue.

On the basis of this work, the thesis is submitted that routine vaginal smears offer the best means of directing further search for very early invasive cervical cancer and "carcinoma in situ."

DR. WILLIAM E. STUDDIFORD, New York City.—Seven of these cases have been discovered at the Bellevue Hospital during the past year, the main method of detection being

cervical biopsy. We have been assisted by cervical cell smears. With one exception they have not offered any particular problem as to treatment. In two cases, the patients had three or four children. In two, the lesion was present in a cervical stump, while two others had complicating fibroids. One patient, aged 27 years, came to the clinic complaining of sterility, with no other symptom.

DR. WILLIAM F. MENGERT, Dallas, Texas.—Since last September, we have done vaginal smears according to the method of Ayre on some 800 women and have found seven with intra-epithelial carcinoma. Not one of these seven women had either sign or symptom of carcinoma. They were simply routine admissions to our out patient clinic. In each instance, of course, smears were followed by biopsies before subsequent operation was performed. In no instance was any definitive treatment done on the basis of the smear alone. We are using the method of scraping with a spatula and believe that is of value since with an intact epithelium cells may not be recovered by aspiration methods. In one instance, scraping of the cervix revealed the presence of neoplastic cells. In order to localize the lesion, the cervix was then divided into four quadrants and four smears made. Two of them, adjacent of course, showed neoplastic cells; the other two did not. Biopsies were made between those two and the carcinoma discovered.

We are beginning to have some evidence that the origin of carcinoma is at the squamous junction of the lateral margins of the cervix, rather than anterior or posterior.

Finally, though Dr. Telinde needs no further commendation, in our small way everything he said we have found to be entirely correct. Also, I should like to express agreement with Dr. Scheffey that the clinical manifestations are a very short period in the total life cycle of a carcinoma.

DR. JOE V. MEIGS, Boston, Mass.—There is one important thing that has not been mentioned and that is the work of Dr. Harry M. S. Green of Yale University. Apparently cancer is of two types: autonomous, and a type of cancer that progresses through the lymph channels to lymph nodes. If a patient has autonomous cancer, that patient will die. That has been demonstrated in cancer of the breast. We are now attempting to repeat this work in cervical cancer at our hospital. We have had no success as yet but that is one of the investigations we are carrying on.

I think the work of Dr. Telinde in attempting to pick up early preinvasive cancer is of very great significance because if it can be found early it is possible that we can get it before it has shown any invasion into the lymphatics. The chances of cure would be greater than if it had made progress and reached the lymphatics or if it had become invasive or perhaps autonomous.

DR. TELINDE (Closing).—In regard to the treatment, I want again to emphasize that this operation which falls short of the Wertheim operation is done only in these cases of microscopic cancer. If the lesion is big enough to be seen with the naked eye, we irradiate. We chose surgery in this study to get the cervixes for study, to try to decide the question of invasion, and have cut many blocks to do so. The second reason is that in many of the young people, in the twenties, we feel justified in taking the chance of saving an ovary. We have no reason to change our line of treatment at present, but I emphasize that not enough time has elapsed to make our statistics of value to date.

Replying to Dr. Studdiford as to what I would do with that very extensive case, I would say that if a wide cuff of the mucosa was obtained, we would do nothing further. The only cases where we irradiate are those in which we find a rather extensive invasion; in other words, where we have misjudged it clinically. They are not included in our present series.

In regard to cytology, we have had much more experience with biopsy than we have with cytology. One's opinion of the two methods will depend upon the statistics read. In Dr. Meigs' surveys, a larger percentage of cases was found with cytology than with biopsy; at the Memorial Hospital, a higher percentage has been found with biopsy. This is true with us, also, but there is no question that a higher percentage will be found by using both methods, biopsy and cytology, than by using either one method alone.

ADENOCARCINOMA OF THE CERVIX AND OF THE CERVICAL STUMP* †

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THERE were registered in our clinic during the ten years, 1938 to 1947, 1,441 patients with carcinomas of the cervixes or of the cervical stumps. Of this number 50 (3.4 per cent) had adenocarcinomas of the cervixes or of the cervical stumps. (Table I.) Thirty-one other case records, in which the diagnosis of adenocarcinoma of the cervix or of the cervical stump had been listed, were excluded from this report because a careful review of the records and pathology failed to substantiate with conviction the diagnosis of adenocarcinoma. These thirty-one records were reclassified as squamous-celled carcinoma of the cervix or of the cervical stump.

TABLE I. INCIDENCE OF ADENOCARCINOMA OF THE CERVIX (1938-1947)

YEAR	CERVICAL ADENOCARCINOMA	TOTAL CERVICAL CARCINOMA
1938	4	131
1939	1	137
1940	6	142
1941	7	124
1942	4	156
1943	5	162
1944	3	145
1945	7	157
1946	5	146
1947	8	141
10 years (Total)	50 (3.4%)	1441 (100%)

In the 50 patients in this report, 11 (22 per cent) had adenocarcinomas of the cervical stumps (Table V); 39 (78 per cent) had adenocarcinomas of the cervix.

Incidence: Our incidence of adenocarcinoma of the cervix or of the cervical stump is 3.4 per cent.

Norris,¹ in 1936, collected from the literature 9,509 cervical carcinomas in which 542 (5.7 per cent) adenocarcinomas were diagnosed. In this series, the incidence of adenocarcinoma of the cervix was given by Keller² as 1.62 per cent; by Pankow³ as 1.9 per cent; by Healy⁴ as 2.7 per cent; by Martzloff⁵ as 5.4 per cent and by Bartlett and Smith⁶ as 11.7 per cent.

Masson,⁷ in his report of 3,273 patients with carcinomas primary in the cervix, listed 2,744 squamous-cell carcinomas and 176 adenocarcinomas. Nils-son,⁸ in 1935, reported 80 patients with adenocarcinomas of the cervix. Cham-

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bers,⁹ in 1935, reported 728 patients with carcinomas of the cervix in whom 223 had unsuitable classification for reporting. Of the remaining 500 patients, 450 had squamous-celled carcinomas and 50 had adenocarcinomas. Crossen¹⁰ found in 121 carcinomas of the cervix, 108 squamous-celled carcinomas and 13 adenocarcinomas. Diddle and Bennett¹¹ in their report on cancer of the cervix in Dallas, Texas, in the years 1936 to 1946, had records of 992 patients in whom cervical carcinomas were diagnosed; 932 were diagnosed as squamous-celled carcinomas and 60 as adenocarcinomas. Simpson et al.,¹² in 1942, found in their institution that there was one adenocarcinoma for every 26 squamous-celled carcinomas and reported 63 adenocarcinomas of the cervix. Numerous other reports may be found in the literature.

Age.—The youngest patient in our series was 27, the oldest 77 years of age. Between the ages of 20 and 40 years, there were 19 patients; between 40 and 70 years, there were 30 patients. Waters¹³ reported adenocarcinoma of the cervix in a girl of 7 months. Pollack and Taylor¹⁴ reviewed the literature for carcinoma of the cervix in women 20 years of age or younger, and found 30 patients. Of these 30 patients, 22 had adenocarcinomas of their cervixes and the authors added a patient, aged 18 years, who had adenocarcinoma of the cervix. In general, our age grouping follows the groupings reported in the literature but our youngest patient was 27 years of age. General data are also given in Table II.

TABLE II. ADENOCARCINOMA OF THE CERVIX OR OF THE CERVICAL STUMP

AGE	NO.	MARITAL STATUS		RACE		PARITY	
20-30	5	Married	37	White	36	Nulliparous	15
30-40	14	Single	6	Indian	1		
40-50	14	Widowed	4	Negro	13	Multiparous	35
50-60	10	Divorced	3				
60-70	6						
70-77	1						
Totals	50		50		50		50

CLINICAL STAGES						
I	-	-	-	-	-	8
II	-	-	-	-	-	19
III	-	-	-	-	-	18
IV	-	-	-	-	-	5
Total						50

Clinical Stages.—(Table II.) The League of Nations Classification was used in expressing the clinical stages of the carcinomas. When the clinical stage was questionable, as, for example, Stage I or Stage II, the former was used. The relationship of the clinical stages to the problems of interpretation of the pathology and to those problems of treatment and ultimate salvage will be discussed in the brief section on pathology.

TABLE III. DURATION OF SYMPTOMS (PATIENT'S RESPONSIBILITY), DELAY IN TREATMENT (DOCTOR'S RESPONSIBILITY)

DURATION OF SYMPTOMS	
Average	9 months.
Longest	24 plus months
Shortest	1 month
DELAY IN DIAGNOSIS AND TREATMENT	
Average	10 months
Longest	24 months
Shortest	1 month

Duration of Symptoms and Delay in Diagnosis and Treatment.—In Table III are shown the data on the duration of symptoms, on the delay in diagnosis, and on the delay in starting treatment. As will be noted, the average duration of symptoms was nine months and the average delay in diagnosis and treatment was ten months. These delays are greater than those reported by Miller¹⁵ in his reports on cervical carcinomas. In Table IV are given the clinical stages of the carcinomas found in the 14 patients with known delays in diagnosis and treatment and also the results in these 14 patients.

TABLE IV. PATIENTS WITH OR WITHOUT DELAY IN DIAGNOSIS AND TREATMENT

		PATIENTS
No Delay in Diagnosis or Treatment		30
Unknown Delay in Diagnosis or Treatment		6
Known Delay		14
Total		50

PATIENTS WITH KNOWN DELAY	
Stage I	1
Stage II	4
Stage III	6
Stage IV	3
Total	14

RESULTS	
Living	1
Unknown	6
Terminal Stage	5
Dead	2
Total	14

Patients With Previous Supravaginal Hysterectomies.—Table V lists the eleven (22 per cent) patients who had had supravaginal hysterectomies performed elsewhere. The first six (54.4 per cent) of these eleven patients were considered by us to have had carcinomas present in the cervixes at the time of the operation.

TABLE V. PATIENTS (11) WITH PREVIOUS SUPRAVAGINAL HYSTERECTOMIES

PATIENT	STAGE	TIME LAPSE FROM OPERATION TO DIAGNOSIS OF MALIGNANCY
M. M.	II-III	3 months
H. W.	II-III	6 months
L. D.	III	6 months
O. B.	II	6 months
L. H.	IV	11 months
M. R.	III	14 months
R. S.	IV	6½ years
A. B.	III	8 years
L. M.	II	20 years
P. H.	III	26 years
M. W.	II	27 years

If either squamous-celled carcinomas or adenocarcinomas are found in cervical stumps within twenty-four months following supravaginal hysterectomies, we have assumed that the carcinomas were present at the time of operations. We realize that this is an arbitrary concept but it does give us some working rule. In view of the attitudes now expressed on "carcinoma in situ" and "preinvasive carcinoma" of the cervix, it is probable that even those patients who develop carcinomas in the stump years after operation, may have had cancer

in the cervix at the time of supravaginal hysterectomy. Certainly, our incidence of squamous-celled carcinomas and adenocarcinomas of the cervical stump strengthens our opinion that panhysterectomies should be performed in preference to supravaginal hysterectomies.

Pathology.—No attempt is made in this report to review the literature concerning the various gradings of adenocarcinomas of cervixes. That differentiation is difficult between squamous-celled carcinoma and some grades of adenocarcinoma of the cervix, has been reported many times. In this report, we discarded 31 case records which were filed as adenocarcinomas, but which, on careful review, had to be reclassified as squamous-celled carcinomas.

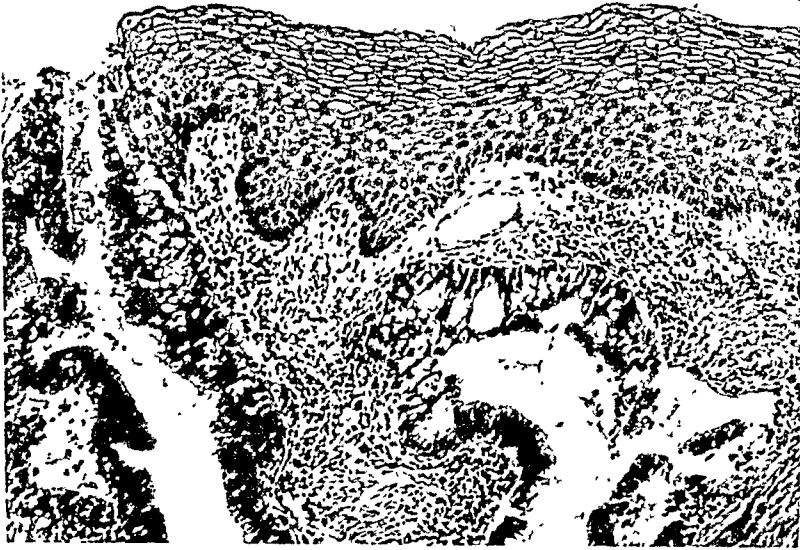


Fig. 1.—Cervical biopsy. Adenocarcinoma of cervix with glandular carcinoma beneath normal squamous epithelium. Low power.

In general, our attempts at grading follow Broders'¹⁶ criteria. The adenomatous growths with good differentiation are listed as Grade I; Grades II and III represent greater degrees of de-differentiation with departure from the normal pattern. Grade IV shows marked degree of anaplasia and unripeness of the cells. As stated by Novak,¹⁷ the personal equation which may enter into the classification in Stages II and III "carries with it no special clinical hazard." His discussion summarizes our attitude in the grading of these adenocarcinomas.

Norris¹ has reviewed the early literature on the various classifications proposed and on the question of the radio-sensitivity or nonradio-sensitivity of adenocarcinoma. Ward¹⁸ and Healy¹⁹ do not consider adenocarcinoma more radio-resistant than squamous-celled carcinoma.

Warren¹⁹ noted the close correlation between the histologic grades of carcinomas and the distribution of metastases. He stressed, however, that the histologic grading was of little value in determining the individual prognosis. The histologic grading was of value in determining radio-sensitivity of the neoplasm and in determining whether the neoplasm was likely to cause metastases. He stated that, as a rule, the more rapidly growing, more anaplastic, and more malignant tumors were sensitive to radio therapy and, therefore, cure of the local growth was common. However, their ability to cause early and wide metastases and infiltrations made them unsatisfactory tumors to treat with radium or other treatments. In his review of the autopsy protocols of 132 pa-

tients who had carcinomas of the cervixes, 11 had adenocarcinomas. No metastases were found in one, the regional nodes were involved in six, the distant nodes were involved in six and the lungs and liver were involved in two.

Behney,²⁰ in his report on 166 autopsies performed on patients with advanced carcinoma of the cervix, also stated that the more anaplastic types of neoplasms were prone to cause more frequent metastases.

Simpson et al.¹² considered the more differentiated neoplasms more radio-resistant. Their rate of growth was slow and they tended to remain localized, and, therefore, a higher percentage of cures might be expected. The anaplastic or de-differentiated neoplasms, although more radio-sensitive, showed more rapid growth, wide infiltration, and early metastases with resultant low cure rates.

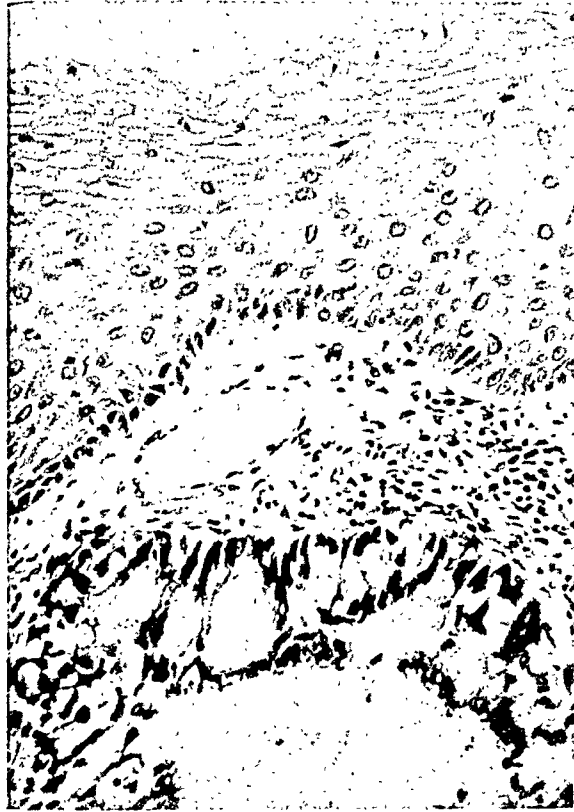


Fig. 2.—Cervical biopsy. Adenocarcinoma of cervix with glandular carcinoma beneath normal squamous epithelium. High power.

We feel that the clinical stage of a neoplasm and the histologic grading are both important in the ultimate salvage.

The number of reports on autopsies done on patients dying with squamous-celled carcinomas and adenocarcinomas of the cervixes is strikingly small. Some method should be evolved which would permit the hospitalization of patients in the terminal stages of cancer. The reaction, or lack of reaction, to radiotherapy or operative therapy might be studied thoroughly, intelligently, and carefully.

Martzloff's²¹ experience with cervical biopsy material is also instructive. He had the opportunity to compare the biopsy tissue with the tissue removed at hysterectomy in 70 patients with epidermoid carcinoma of the cervix. In one third, the biopsy material was insufficient to make possible a definite classification. We have for years discontinued the use of "biopsy of the cervix" and have substituted "multiple biopsies of the cervix and multiple biopsies of the endocervix."

The use of repeated and repeated Papanicolaou histocytologic smears and of repeated and repeated biopsies of the cervix and endocervix may be the answer to early diagnosis and to correct gradation of the carcinomas.

Papanicolaou smears were done on seven patients in this series of fifty.

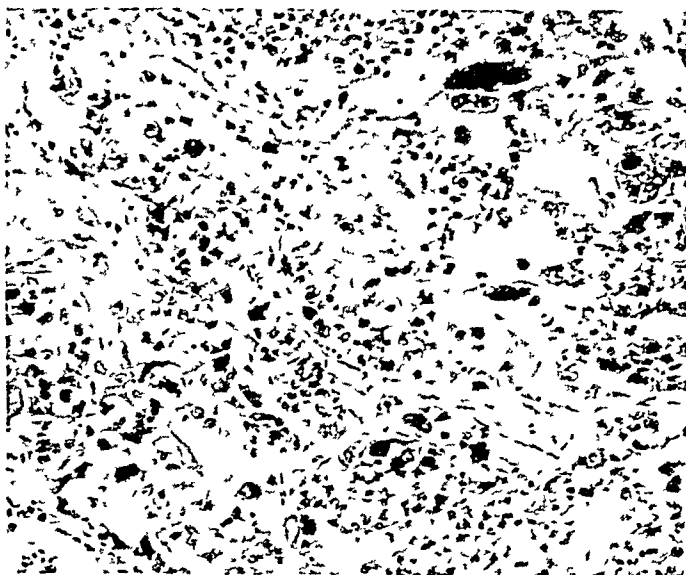


Fig. 3.—Wertheim, cervix. Glandlike structures and anaplastic undifferentiated carcinoma post x-ray and radium.

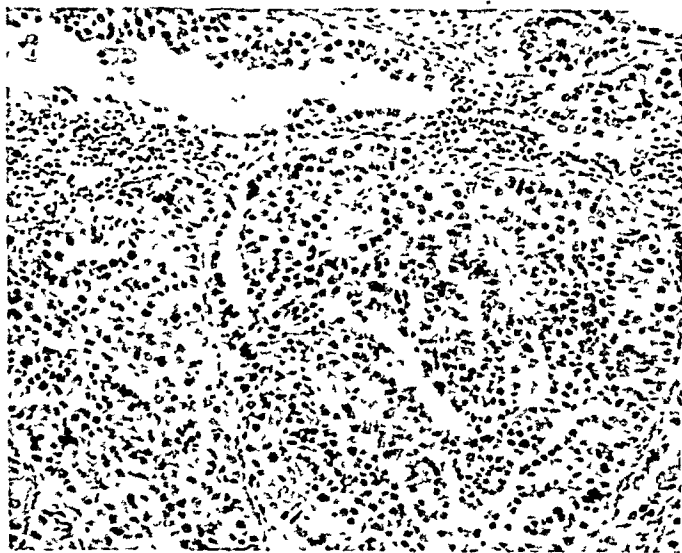


Fig. 4—Biopsy of cervix. Adenocarcinoma in cervical biopsy after inadequate irradiation over two-year period.

Type V smears were reported in four patients; type IV smears in one patient; type III in two patients. Adenocarcinoma was diagnosed as such in three; as questionable adenocarcinoma in two and as squamous-celled carcinoma in two. With improvement in the histocytologic techniques and with the increasing experience of the workers in these techniques, we believe that routine

“screening” of all women 30 years of age or over who come to our clinic will be useful in detecting possible carcinomas of the uterus at earlier stages than we have seen in the past.

Table VI gives the results of irradiation therapy only. Of 29 patients, only 18 received what we term “adequate” x-ray and radium therapy. Of these 18

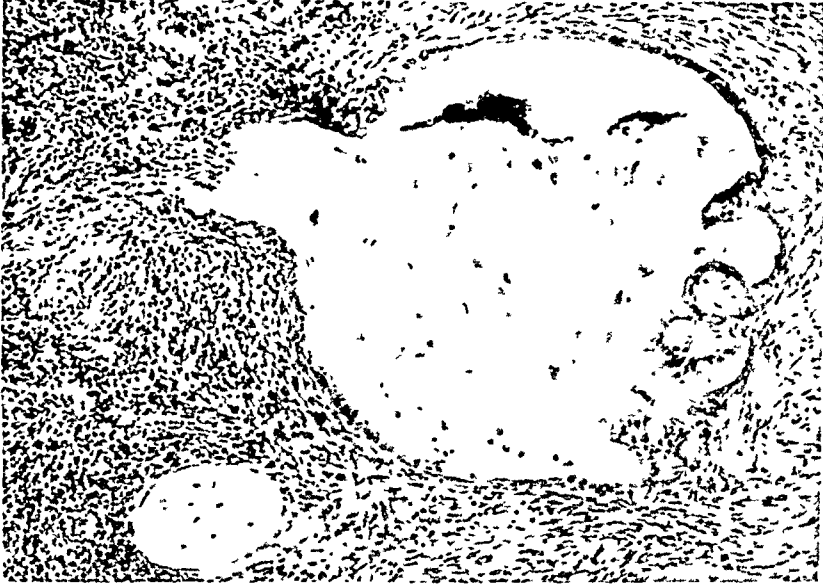


Fig. 5.—Wertheim, lymph node. Mucus-producing glandular pattern. Definitely adenocarcinoma.



Fig. 6.—Wertheim, lymph node. Metastasis with gland pattern and solid tumor nests.

patients, but two (11.1 per cent) are living, whereas eight are in the terminal stages of cancer. Two are dead of cancer and six are listed as unknown, i.e., presumed to be and counted as dead.

TABLE VI. RESULTS OF IRRADIATION THERAPY ONLY

TREATMENT	NO. OF PATIENTS	RESULTS			
		LIVING	TERMINAL STATE	DEAD	UNKNOWN
Adequate x-ray and radium	18	2	8	2	6
Inadequate x-ray and radium	5	0	4	0	1
Adequate x-ray only	5	0	2	1	2
Adequate radium only	1	0	0	0	1
Totals	29	2	14	3	10

Five patients received "adequate" x-ray therapy only and two are in terminal stages, one is dead of cancer, and two are listed as unknown, i.e., presumed to be and counted as dead.

One patient received adequate radium therapy only and is listed as unknown, i.e., presumed to be and counted as dead.

Five patients received inadequate x-ray and inadequate radium therapy. Four are in the terminal stages and one is listed as unknown, i.e., presumed to be and counted as dead.

The patients are usually responsible for the failures in the attempts to give what we term adequate irradiation therapy. The intelligent patients are co-operative in the matter of permitting careful therapy and good follow-up care. Many of the uninformed patients are remiss in following orders for therapy and follow-up.

TABLE VII. PATIENTS TREATED WITH X-RAY, RADIUM AND OPERATION WITHOUT KNOWN SALVAGE (DEAD, TERMINAL STATE, UNKNOWN)

PT.	STAGE	IRRADIATION THERAPY			OPERATIVE PROCEDURE	PATHOLOGY		RESULTS
		TOTAL R.	VAGINAL CONE	RADIUM MG. HR.		CERVIX	POSITIVE NODES	
H. W.	(Stump) II-III	18,500	3000	3600	Rad. Removal of Stump Radical Lymphaden.	+	L. iliac	Dead
L. M.	(Stump) II	0	0	0		+	0	Terminal
S. R.	I-II	Post-op. 10,600	0	6000	Rad. Hyst. Radical Lymphaden.	0	Bilat. Obt. & Iliacs	Dead
B. G.	III-IV	13,600	3000	0		+	Lt. Obt.	Unknown
M. B.	III	Post-op. 7,450	0	0		Cervix Uterus Vagina	Bilat. Obt. & Iliacs	Terminal
L. F.	IV	0	0	Unknown amt. 17 yrs. prior	Rad. Hyst.	+	Abdo. Car- cinoses	Dead
F. B.	III-IV	9,200	500	3800		+	0	Dead
L. F.	I-II	10,500	0	4350		0	0	Unknown
L. D.	(Stump) III-IV	11,100	0	3100	Rad. Removal of Stump.	Cervix Vagina	0	Terminal
N. M.	(Stump) II-III	10,000	0	0		0	0	Dead

Table VII lists those patients treated with x-ray, radium, and operation in whom there was no salvage.

Two patients had radical removals of the cervical stumps and radical pelvic lymphadenectomies. One of these two had adequate preoperative x-ray and radium therapy. The pathology report showed cancer in the cervix and cancer in the left iliac nodes. The patient died later of cancer. The other patient received no x-ray or radium therapy before the radical operation for removal of the stump and the radical pelvic lymphadenectomy. She had cancer in the cervix but no cancer in the nodes. The patient was in the terminal stages of the disease when last seen.



Fig. 7.—Wertheim, lymph node. Metastatic adenocarcinoma to the node; post irradiation.

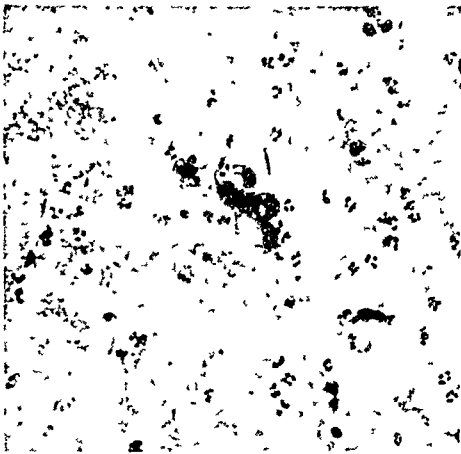


Fig. 8.

Fig. 8.—Papanicolaou smear. Group of vacuolated adenocarcinoma cells.



Fig. 9.

Fig. 9.—Papanicolaou smears. Single large group of adenocarcinoma cells.

Three patients had radical hysterectomies and radical pelvic lymphadenectomies.

One of these patients had adequate preoperative x-ray therapy only and cancer was found in the cervix and in the left obturator nodes. She is presumed to be dead of cancer. The next patient received adequate preoperative radium therapy only. The cervix showed no cancer but cancer was found bilaterally in the iliac and obturator nodes. She received adequate postoperative x-ray therapy. The patient died later of cancer. The last of these

three patients received no preoperative x-ray or radium. The cervix, the lower uterus, and the vagina showed cancer and cancer was found bilaterally in the iliac and obturator nodes. Adequate postoperative x-ray therapy was given. The patient died later of cancer.

Three patients had radical hysterectomies but did not have radical lymphadenectomies performed. The first patient had received an unknown amount of radium seventeen years before her admission. No preoperative x-ray or radium were given. Operation showed adenocarcinoma of the cervix and of the glands and of the other pelvic structures. She died later of cancer. The second patient received inadequate x-ray and radium therapy preoperatively. Pathology showed adenocarcinoma of the cervix. She died later of cancer. The last patient of these three received adequate x-ray but inadequate radium preoperatively. Pathology showed no cancer in the cervix. She cannot be traced and is presumed to be and is counted as dead.

Two patients had radical removal of the cervical stumps but no radical lymphadenectomies. The first patient received adequate preoperative x-ray and inadequate preoperative radium. Pathology showed carcinoma of the cervix and of the vagina. She is now in the terminal stages of cancer. The second patient received adequate preoperative x-ray therapy but no preoperative radium. The pathology report showed no cancer in the cervical stump. The patient died later of cancer.

Table VIII is the summary of the treatment of the 13 patients who are living.

TABLE VIII. SUMMARY OF TREATMENT IN LIVING PATIENTS (13)

PT.	CLINICAL STAGE	IRRADIATION X-RAY			OPERATIVE PROCEDURE	OPERATIVE PATHOLOGY		MONTHS LIVING
		TOTAL R.	CONE	RADIUM MG. HR.		CERVIX	NODES	
M. R.	III	8,604	5040	6000	0	0	0	36
G. C.	II	14,800	3500	6312	0	0	0	96
B. W.	II-III	*8,800	0	0	Radical Hyst.	+	0	14
M. S.	II	13,600	3000	3600		0	0	39
I. C.	II-III	9,600	0	5000		+	0	61
M. W.	cerv. stump II	13,500	3000	0	Rad. Removal of cervical stump	+	0	94
C. S.	I	0	0	0	Rad. Hyst.	+	0	7
A. R.	II	0	0	0	Rad. Lymphad.	+	0	8
A. E.	II	0	0	0		+	0	8
R. M.	I	*10,600	0	0		+	0	24
F. G.	II	7,063	5200	5940		0	Left iliac	60
J. S.	II	13,400	4000	5200		0	0	64
I. W.	I-II	10,300	5200	0		0	0	72

*Postoperative x-ray.

The first two patients had adequate x-ray therapy including adequate x-ray by vaginal cone and adequate radium therapy. No operations were done. The first patient has lived 36 months and the second 96 months.

The third patient had no preoperative x-ray or radium therapy prior to radical hysterectomy and did not have radical pelvic lymphadenectomy. The cervix showed cancer. She received inadequate x-ray therapy postoperatively. The patient is living 14 months following therapy.

The fourth patient had preoperatively adequate x-ray therapy which included 3,000 r. by vaginal cone. She received inadequate preoperative radium. A radical hysterectomy was done. The patient is living 39 months after treatment. The cervix showed no cancer.

The fifth patient had inadequate preoperative x-ray therapy with no vaginal cone therapy and inadequate preoperative radium therapy. A radical hysterectomy was done. The cervix was positive for cancer. She is living 61 months after completion of treatment.

The sixth patient had adenocarcinoma of the cervical stump. She received adequate preoperative x-ray therapy including 3,000 r. by vaginal cone. She had no preoperative radium therapy. She then had radical removal of the cervical stump. The stump showed cancer. She is living 94 months following therapy.

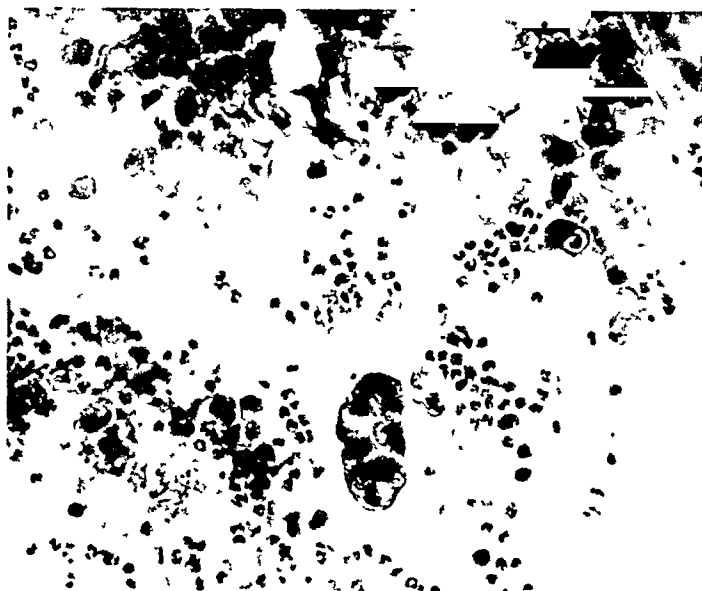


Fig. 10.—Papanicolaou smears. One group of vacuolated adenocarcinoma cells. Edge of large sheet of adenocarcinoma (undifferentiated).

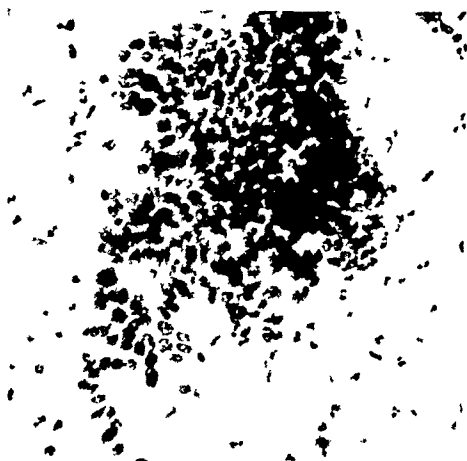


Fig. 11.



Fig. 12.

Fig. 11.—Papanicolaou smear. Large sheet of small adenocarcinoma cells.

Fig. 12.—Papanicolaou smear. Single clump of adenocarcinoma cells

The seventh, eighth, and ninth patients had no preoperative x-ray or radium therapy and had radical hysterectomies with radical pelvic lymphadenectomies. The cervixes were all positive for cancer, but the nodes showed no cancer. None received postoperative x-ray therapy. The three are living 7, 8, and 8 months, respectively, following therapy.

The tenth patient received no preoperative x-ray or radium therapy and had a radical hysterectomy and radical pelvic lymphadenectomy. The cervix was positive for cancer. No cancer was found in the nodes. She received 10,600 r. of x-ray, postoperatively. She is living 24 months after completion of therapy.

The eleventh, twelfth, and thirteenth patients all received adequate preoperative x-ray therapy, including vaginal cone. Number 11 and Number 12 received preoperatively 5,940 mg. hr. and 5,200 mg. hr. of radium, respectively. Patient 13 received no preoperative radium therapy. Radical hysterectomies and radical pelvic lymphadenectomies were done on all three. The cervixes of the three showed no carcinoma. The eleventh patient had carcinoma in the left iliac glands; the twelfth and thirteenth patient had no carcinoma in the glands. They have lived respectively 60, 64, and 72 months.

TABLE IX. RESULTS

CONDITION	NUMBER OF PATIENTS	PER CENT
Living	13	26
Terminal State	18	36
Dead	8	16
Unknown	11	22
Total	50	100

Table IX summarizes the results for the 50 patients. Eight (16 per cent) are known to be dead; eleven (22 per cent) are listed as unknown, i.e., presumed to be and counted as dead. Eighteen (36 per cent) were in the terminal stages of cancer when last seen.

Of the thirteen (26 per cent) patients living at present, only six (12 per cent) have reached or have passed the five-year mark at which we list them as "presumptive" cures.

Complications

There were no deaths due to irradiation or operative treatment.

Pyometra occurred in ten patients and responded to drainage.

Vesicovaginal fistulas occurred once as the result of carcinomatous infiltration and once as the result of operation.

Ureteral strictures were found in two patients and were dilated.

Pyelonephritis occurred in two patients.

Rectovaginal fistulas occurred twice, once as the result of cancer extension and once as a postoperative complication.

Proctitis developed in five patients. Rectal stricture was found in one patient. Thrombophlebitis occurred twice; once postoperatively and once spontaneously. Two patients (G. C. and I. C.) are interesting in that each developed adenocarcinoma of the bladder after treatment for adenocarcinoma of the cervix.

G. C., Stage II, adenocarcinoma of the cervix, was treated in 1940 with 11,300 r. through 2 anterior and 2 posterior ports and 3,500 r. by vaginal cone. She received 6,312 mg. hr. of radium. No operation was done. In 1942, adenocarcinoma of the bladder was diagnosed and the cancer was treated with radium. The patient is now living, eight years after the treatment for adenocarcinoma of the cervix and six years after treatment of the adenocarcinoma of the bladder.

I. C., Stage III, adenocarcinoma of the cervix, was treated in 1943 by 9,600 r. through 2 anterior and 2 posterior ports. No vaginal cone therapy was given. She received 5,000 mg. hr. of radium in 1943. In 1943, she had radical hysterectomy. In 1944, adenocarcinoma of the bladder was diagnosed and was treated with radium. The patient is living and well five years after the radiation therapy and operation for adenocarcinoma of the cervix and vagina and four years after the treatment of the adenocarcinoma of the bladder.

Summary

1. The incidence of adenocarcinoma of the cervix or of the cervical stump was 3.4 per cent in a series of 1,441 patients with carcinomas of the cervixes

or of the cervical stumps who were registered in the ten years, 1938 to 1947.

2. Forty-two of the adenocarcinomas, when first seen, were Stage II, III, or IV. Histologic grading was, in all probability, inaccurate but the incidence of undifferentiated carcinomas was high.

3. The average duration of symptoms before the patients were seen was nine months; the average delay in diagnosis and the starting of treatment was ten months.

4. There were eleven (22 per cent) patients in this series of 50 who had adenocarcinomas of the cervical stumps. This incidence, with our high incidence of squamous-celled carcinomas in cervical stumps, strengthens our conviction that panhysterectomies are preferable to supravaginal hysterectomies.

5. "Adequate" x-ray and radium therapy, as the only method of treatment, was given 18 patients. Two (11.1 per cent) are living; one has lived 36 months and one 96 months with no evidence of disease. The other 16 patients are either in the terminal stages of the disease, are dead, or are lost and counted as dead of cancer.

6. Five patients had radical hysterectomies or radical removals of the cervical stumps and radical pelvic lymphadenectomies. Cancer was found in the cervixes of four patients, in the uterus and vagina in one, and in the pelvic lymph nodes in four. All of these patients died of cancer.

7. Seven patients had radical hysterectomies and radical pelvic lymphadenectomies. In one the left iliac nodes showed cancer; in the other six there were no positive nodes. This patient with positive nodes has lived 60 months and two other patients have lived 64 and 72 months, respectively, without evidence of cancer. The four other patients have lived 24, 8, 8, and 7 months, respectively, without evidence of cancer.

8. There were no deaths in this series from either irradiation therapy or from operations.

9. Of the thirteen (26 per cent) patients living at present without evidence of disease, only six (12 per cent) have reached or passed the five-year limit at which we list the patients as "presumptive" cures.

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Discussion

DR. KARL MARTZLOFF, Portland, Oregon.—The adenocarcinomas of the cervix which Dr. Carter described, I assume, represent tumors that occur primarily in the cervix or the residual cervical stump after supracervical hysterectomy. Therefore, I would like to emphasize additionally the observation that adenocarcinoma of the cervical stump may on occasion represent remanifestation of an endometrial cancer of the more proximal uterus that has been either overlooked or improperly treated by supracervical hysterectomy.

I agree thoroughly with his observations concerning the difficulties involved in the diagnosis of some specimens of cervical adenocarcinoma when the tumor shows a high degree of differentiation or when aggregations of Gärtner duct tubules showing some deviation from normal provide problems of interpretation. The difficulty here is considerably different from the one encountered in some of the argumentative problems evolving about the epidermoid cancers. In the latter, as was demonstrated this morning by Dr. TeLinde, there is ordinarily no difficulty in deciding that a given zone in superficial stratified epithelium or in the squamous cell metaplasia of a gland represents a neoplastic change.

When differences of opinion occur, the point at issue then generally centers about the decision as to whether the neoplasia represents merely a noninvasive carcinomatoid change or whether actual invasion and established cancer exist.

However, where well-differentiated adenocarcinoma or what are interpreted as altered Gärtner ducts are concerned one's difficulty is immediately apparent, for the perplexing question which confronts one now is, are these glands neoplastic, or is this a picture of bizarre benign proliferation? In some such instances, irrespective of the diagnosis under which a lesion is finally catalogued, the true answer in my experience may be never attained until perchance exploratory operation or death proves the malignant character of a process previously considered as benign.

The foregoing considerations, I believe, explain the profound variations that occur in statistical reports concerning the comparative incidence of adenocarcinomas among cervical cancers. Percentages that vary from 1.6 to 11.7 per cent are far removed from normal statistical variation and error and, therefore, represent fundamental differences in criteria utilized by different individuals for the diagnosis of adenocarcinoma. Dr. Carter's figures admirably demonstrate this point, for among 81 patients who had been catalogued originally as having adenocarcinoma of the cervix, only 50 of those diagnoses withstood the scrutiny of a critical review. Although this discussion does not concern the epidermoid cervical cancers, I believe it is pertinent that a similar critical review by many laboratories for this group of tumors would also reveal little factual support for some of their diagnoses.

The amount and manner of obtaining tissue for biopsy are also inextricably involved in the diagnostic problem. Small pieces of tissue obtained with the endothermy unit by so-called conization are, I believe, an open invitation to error. The heat which causes outright readily recognizable peripheral tissue destruction also permeates the underlying tissue for varying depths and produces here bizarre nuclear changes that are often difficult of interpretation. Likewise the minute tissue fragments obtained with a small biopsy punch, because of their inadequacy, are a source of real concern to many of our pathologists and not infrequently preclude a definitive diagnosis where it might otherwise have been feasible. It is a fair assumption that errors occur at both extremes of the statistical scale and it is doubtful that any board of expert gynecologic pathologists passing judgment on adequately obtained and prepared tissues could wholly eliminate such differences.

Variations in diagnostic accuracy, as a corollary, must then reflect the ultimate rate of cure reported following therapy in such a group of selected patients. I am sure that such diagnostic misinterpretation must play a role in explaining, for example, some of the dis-

crepancies reported concerning the radiation sensitivity or resistance of this particular class of tumors as well as some of the cures reported from the use of comparatively minute doses of radium radiation.

In conclusion, I would like to call particular attention to the relatively uncommon mucoid type of cervical adenocarcinoma. This, I believe, is both highly radiation resistant and generally slowly progressive. It should be subjected, I believe, to the radical operation without waiting for postradiation remanifestation as long as it is in an operable stage, namely, League of Nations clinical Stages 1 and 2 or, possibly 3. Remanifestations of these tumors after temporary suppression with intensive radiation therapy may be difficult to recognize because curettage may bring away no recognizable tissue. However, a recurring mucoid vaginal discharge should arouse suspicion which may be confirmed by obtaining with the scalpel a large segment of tissue for biopsy.

DR. GEORGE GRAY WARD, New York City.—At the Woman's Hospital in New York we have been interested in carcinoma of the stump and its treatment.

In 879 carcinoma of the cervix cases seen from 1919 to 1940, 61 were stump cases following a previous hysterectomy or 6.7 per cent; 49 of these were observed for five years after treatment with 21 living, or 42.8 per cent; 20 were observed for ten years, 10 of whom were living, or 50 per cent.

In the same period of five years, our salvage of all carcinoma of the cervix cases was 28.5 per cent.

Thirty-two of these stump cases arose three years after hysterectomy, or 3.6 per cent, which is about the usual average in other clinics. Sixteen were classed as early, and 45/ were advanced; 47 were classified as squamous carcinoma, of whom 20 survived five years, or 44 per cent, and 9 survived ten years, or 20 per cent.

Twelve cases were classified as adenocarcinoma, or 2 per cent; two survived five years, or 20 per cent; and only one survived ten years.

In a recent analysis of 236 cases of carcinoma of the cervix originating from 1933 to 1940 observed for five years, there was a relative survival of 35 per cent.

Of these 236 cases, fifteen were stump carcinoma, or 6.4 per cent with a five-year salvage of 46.7 per cent.

The adenocarcinoma cases averaged as in the previous report.

In our opinion, stump cases as a rule do better with radium treatment than cases in which the whole uterus is present. Dr. Scheffey and Dr. Behney have also reported similar results.

DR. CARTER (Closing).—Certainly the main point is early diagnosis. Diagnosis of carcinoma may be made early by taking repeated histocytologic smears and by repeated biopsies of the cervix and endocervix.

The contributions of the Fellows of this Society to the subject of cancer have been real. We will be interested in seeing whether we will be able to show a 25 per cent cure rate in adenocarcinoma of the cervix. In patients who are good operative risks, we feel that there is a place for the radical hysterectomy and the radical pelvic lymphadenectomy. If patients with metastatic cancer in the glands can be proved to be cured by the operative procedure, then the operative procedure should have a place in the treatment.

ADENOCARCINOMA OF THE UTERUS

Observations on Treatment and Histologic Findings Following Intracavitary Radiation

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DUE, in a large measure, to the recent augmented activities of the American Cancer Society, the people of this country are becoming increasingly "cancer conscious." The value of this work is manifested by the popular demand for prophylactic examination for the early detection of malignancy. Already the detection centers are crowded with those requesting investigation and the increasing number of early malignant lesions discovered attests the value of this work. With the existing educational program, women are more cognizant of the meaning of menstrual irregularities and atypical forms of vaginal bleeding in the latter years of life. As is well known, women with menstrual dysfunction at this time are frequently lulled into a false sense of security, believing it to be a normal climacteric event, and refrain from pelvic examination. Today, an increasing number of women come biannually for pelvic and breast examinations and many are realizing that abnormal bleeding, although painless, requires prompt and competent investigation. Early examination for the detection of malignancy is of the essence and is of especial importance in adenocarcinoma of the uterus. In the early stages of this condition the pelvic examination may be entirely negative, minimal bleeding may be the only danger signal and the diagnosis made only by examination of the endometrium. In the past it was not uncommon for the roentgenologist to treat supposed menopausal bleeding with roentgen therapy without first having obtained a definite diagnosis by curettage. However, with increasing knowledge, this dangerous procedure has decreased to a minimum.

Analysis of Clinical Factors

As is well known, the early symptoms of adenocarcinoma may be quite minimal, the only indication of pathology being painless bleeding, either in the form of menorrhagia or metrorrhagia. This symptom may exist for a long period of time and the condition still remain in the realm of operability. Small bleeding associated with normal pelvic findings may be interpreted as a manifestation of the climacteric or occurring during the childbearing age as due to hyperplasia of the endometrium or to some other type of dysfunctional bleeding. Adenocarcinoma of the corpus frequently arises in the region of the uterine cornu and from there may migrate to the external os of the cervix being confined primarily to the endometrium with varying degrees of myometrial involvement. The growth may also advance rapidly through the wall of the uterus

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

and by lymphatic dissemination soon infect the aortic group of glands by way of the ovary and infundibuliform lymphatics. The slowly growing tumor frequently reaches considerable size, with resulting enlargement of the uterus due to an intracavitary as well as myometrial invasion. It can be readily seen that an enlarged uterus not caused by an associated myoma denotes an advanced lesion with poor prognosis. The above statement is not always the rule; the young, active lesion, with a normal sized uterus, may have more extensive glandular invasion than that observed with the large uterus.

The advanced lesion may be associated with ascites due to generalized carcinomatosis resulting from transmigration of the growth through the myometrium with fragmentation of the papillary excrescences. The senior author has seen such late manifestations in two women who refused investigative curettage. When they were first seen the pelvic examinations were normal; however, on subsequent investigation months later, the developing abdominal distention proved to be due to ascites. At laparotomy, both patients showed extensive diffuse malignant implants originating from the growths on the surface of the uterus. Frequent paracentesis was necessary for comfort and cycles of deep roentgen therapy proved of no avail.

With the increasing number of women applying for investigation, the incidence of adenocarcinoma in relation to carcinoma of the cervix seems to be increasing. This increase has been particularly noted during the past few years and is the result, in a large measure, of increased educational programs developed under the aegis of the American Cancer Society and the Federal Government. With us the ratio is approximately 1 to 5.

It is usually stated that adenocarcinoma occurs more frequently in the nulliparous woman than in the multiparous. However, our studies show that 64.6 per cent of the patients had borne children, whereas 35.4 per cent were barren. This lesion also occurs as a rule in the more aged and it should be noted that 85 per cent were present during the menopause or thereafter and the remaining during the childbearing years. Our youngest patient was 23 years of age, the oldest 78.

The authors feel that emphasizing the occurrence of malignancy in specific age groups could be harmful for the physician may feel that the youth of the patient seeking aid for painless bleeding would preclude the possibility of corpus carcinoma and therefore not advise a diagnostic curettage.

In this study, 124 patients seen between 1932 and 1947 have been reviewed. The analysis according to age groups is as follows:

AGE	NUMBER	PER CENT
Under 35	5	4.0
35-45	10	8.1
46-60	62	50.0
61 or over	45	36.3
Age unknown	2	1.6
Total	124	100.0
The age of the youngest		23 years
The age of the oldest		78 years
The average age		55.9 years

It has been stated that the incidence of corporeal carcinoma is about equal in the white and Negro races. Our statistics show that this lesion occurred in 117 whites as compared to 6 in the Negro race. In one, the race was not mentioned. The only explanation we can offer for this wide variant is that the vast majority were private patients. This finding is of interest, however, for our

gynecologic clinic is predominantly of the colored race and if the incidence is equal there should be a greater number of blacks. Of the 124 patients studied, approximately 10, or 8 per cent, were of the Jewish race.

Differential Diagnosis

Curettage is the sine qua non in the diagnosis of corpus carcinoma. Conditions which produce painless bleeding with a normal pelvic examination are not too numerous; however, hyperplasia of the endometrium and other forms of dysfunctional bleeding are the most frequent lesions that have to be excluded. At times, atypical forms of endometrial hyperplasia are extremely difficult to differentiate from adenocarcinoma as brought out by Novak¹ in a recent publication. If doubt exists, the condition should be treated as malignant.

Other causes such as endometrial polyps and submucous myomas may be the source of painless bleeding. This latter condition can frequently be diagnosed with the curette. With distortion of the uterine cavity resulting from myomas a satisfactory curettage is difficult due to areas of inaccessibility. On removal and inspection of the uterus after the most careful curettage, one is often amazed at the amount of untouched endometrium remaining.

Perforation is one of the accidents that may occur, especially in the atrophic menopausal uterus. Of course, if intracavitary radiation had been planned and this mishap occurs, radium should not be inserted, as the capsule may even be lost in the abdominal cavity. Such a situation has been reported which necessitated laparotomy for its recovery. We have perforated the uterus on a number of occasions with no untoward results. On one occasion when perforation was done, the laparotomy, which had previously been planned, made possible the inspection of the puncture wound and we were amazed at the small amount of free blood present. Obviously, if this had occurred in a subinvolved uterus, the amount of bleeding might have been excessive and thus have necessitated a laparotomy.

Prognosis is dependent in a large measure on the clinical extent of the disease and on individual biologic factors that are not clearly understood. The size of the uterus, as already noted, may be helpful in prognosis; here the lesion is often slow growing, invading the myometrium and developing a large intracavitary mass. The lesion may be well advanced prior to the onset of symptoms and in spite of its duration may still be in the realm of operability.

Treatment

With us the treatment of carcinoma of the fundus is divided into two categories dependent upon the condition of the patient, namely the good risk group and the poor risk group.

Treatment of the Good-Risk Patient.—Our routine is as follows: Careful and thorough curettage is carried out under Pentothal anesthesia. We have never been enthusiastic concerning suction curettage. Frozen sections are immediately examined. However, permanent ones are also made, for we have noted on very infrequent occasions that the frozen section may be negative while the permanent ones are positive. This situation makes for embarrassment if the patient has been informed that no malignancy exists. It is best to wait for the permanent section report before making a positive statement.

When a definite diagnosis of malignancy has been determined, multiple applicators containing 10 to 25 mg. of radium are inserted into the uterine cavity until it is quite full. Great care is taken not to perforate the diseased uterine wall. Varying number of capsules are used depending upon the size and con-

formation of the uterine cavity. A total of 4,000 to 4,500 mg. hr. of radium is the usual dosage. However, with a large uterus this may be increased. The filtration is of platinum and iridium and is equivalent to 2 mm. of lead. The several tubes are removed in reverse order so that a "log jam" does not develop. This complication occurred in one instance with breaking of the attached string, and the removal of the free tube was accomplished with great difficulty by probing the uterine cavity under anesthesia. In many cases the intracavitary radiation was accomplished by the use of 100 mg. of radium in a tandem. It is obvious that with this method the distant lesion, or inaccessible one, when associated with a myoma does not receive adequate radiation for we know the lethal ray of radium may extend only 2 to 2.5 cm. from the focal point. Thus, the distant cells may receive insufficient radiation, whereas the center of the lesion may be overirradiated. In order to obtain adequate irradiation, multiple sources are preferable, as shown by the work of Heyman and Benner. Their method consists of introducing small amounts of radium into the uterus until the cavity is completely filled. The results with this method as compared with those obtained with the intrauterine tandem are striking and will be noted below.

From 1914 to 1933, a total of 354 patients were irradiated with radium in tandem using 35 to 45 mg. From this group the five-year survival rate was 45 per cent. Now compare these results with those obtained from the multiple source plan. From 1934 to 1939, a total of 316 patients was treated with a sufficient number of weaker tubes to fill the uterine cavity completely. By this multiple-source method, the five-year survival rate was 65 per cent. The above statistics are quoted from Arneson, et al.² During the period of intracavitary radiation, elevation of temperatures is carefully observed and if there is a sustained elevation to 102° F. radium is removed even before the completion of the application has been reached. Cellulitis and even peritonitis may result from intracavitary therapy. If the uterus is enlarged and there is an associated malodorous discharge, a preliminary cycle of deep roentgen therapy of 4,500 r. may be advantageous for the organ then regresses as does the intracavitary growth and the virulence of the infection tends to abate. This preliminary ray therapy is of especial value when dealing with a large submucous myoma which distorts the cavity and makes efficient radium application difficult or impossible.

Four to six weeks following radiation therapy, a panhysterectomy and bilateral salpingo-oophorectomy are performed. The most propitious time for this procedure is when the radiation effect is optimum. Obviously, this point is difficult to ascertain; one has to deal with many factors, such as cell sensitivity, biologic variation, the size of the lesion as well as of the uterus, etc. If the operative procedure is postponed many more weeks, increased fibrosis with loss of planes of cleavage comes about. Occasionally, rather dense adhesions are encountered binding down the pelvic organs. Some writers feel that radiation tends to increase the operative difficulty as a result of augmented bleeding. The individual variation is so marked that it is difficult to support such an opinion. Undoubtedly, the radiated, postmenopausal uterus undergoes increased obliterative endarteritis and there is a minimal amount of operative hemorrhage, whereas when dealing with a subinvolved uterus prior to the menopause, bleeding may be far more profuse.

Approximately four to six weeks following the laparotomy, a cycle of deep ray therapy of 8,000 r. may be given. This procedure was carried out in 21, or 64.4 per cent of the cases studied. If definite metastasis outside the uterus is found, the subsequent cycle of ray therapy is of definite value, otherwise its efficacy is doubtful.

Treatment of the Poor-Risk Group.—The important conditions placing the individual in this category are as follows: advanced age with general debility, severe renal disease, hypertension with marked cardiac pathology, and obesity. With increasing experience the mechanical difficulty, occasioned by obesity, has become less of a problem. The main essential in the treatment of the very obese patient is a satisfactory anesthesia, preferably by the spinal route. However, if this is not feasible, cyclopropane with curare gives excellent relaxation. We have successfully operated on a number of patients over 250 pounds in weight with little difficulty. Once a positive diagnosis is made by curettage, intracavitary radiation is carried out as described above, the average dosage being between 4,000 and 4,500 mg. hr. using the multiple source technique. Following intracavitary radiation, a cycle of deep roentgen therapy is carried out until a dosage of 8,500 r. has been attained. As stated above, if the uterus is definitely enlarged with a protruding intracavitary growth, a cycle of roentgen therapy before the intracavitary radium is of value as the resulting regression makes for better radium application. We feel that the multiple-source technique is preferable to applying the radium in tandem as has been the custom. The advantages are obvious; for by this method better coaptation between radium and the growth is accomplished. As yet sufficient data have not been accumulated to present a comparative study of these two methods, but several reports, notably the one by Heyman, noted above, strikingly support this opinion.

The comparative results obtained between the good-risk and poor-risk groups over the period 1932 to 1942, were as follows: This study is based on 66 patients. Unfortunately 18 patients could not be included due to inadequate therapy and follow-up. Of this group of 66 patients, 32, or 48.5 per cent, were treated with intracavitary radiation followed by panhysterectomy and bilateral salpingo-oophorectomy. The five-year survival rate was 84.4 per cent with 27 patients living and well. There were five deaths during this period, or a rate of 15.6 per cent. The remaining number of patients, namely the 34 in the poor-risk group, were treated by radiation alone, i.e., intracavitary radiation followed by a cycle of deep roentgen therapy. Of the 34 patients treated, or 51.5 per cent of the total, there was a survival of only seven patients, a percentage rate of 20.6 per cent, twenty-seven, or 79.4 per cent dying from malignancy.

The survival rate of 20.6 per cent obtained by radiation is a poor showing when compared to the results of Heyman. He had a five-year survival rate of 45 per cent with the tandem method of therapy. With the multiple-source technique the survival rate for the same period was 65 per cent. It is fair to deduce, I believe, that if all the patients in the series, i.e., the good-risk and poor-risk, had been treated by intracavitary radiation, the survival rate would have been much higher. See Table I.

From a study of the figures in Table II, it is noted that the greater the maturity of the tumor, the greater the five-year survival rate. The highest rate of salvage was found in the differentiated grade I and II lesions.

TABLE I. FIVE-YEAR SURVIVAL RATE ACCORDING TO TYPE OF THERAPY

Total Number of Patients Treated 1932-1942	84
Number With Inadequate Follow-up and Treatment	18
Number of Patients in This Study	66

TREATMENT	TOTAL NO.	PER CENT	FIVE-YEAR SURVIVAL	PER CENT	DIED OF MALIGNANCY	PER CENT
Combined	32	48.5	27	84.4	5	15.6
Radiation alone	34	51.5	7	20.6	27	79.4
Operation alone	0		0		0	
Total	66	100.0	34	51.5	32	48.5

TABLE II. RELATIONSHIP BETWEEN MICROSCOPIC CLASSIFICATION AND FIVE-YEAR SURVIVAL RATE

Total Number of Patients Treated 1932-1942				84		
Number With Inadequate Follow-up and Treatment				18		
Number of Patients in This Study				66		
GRADE	TOTAL NO.	PER CENT	FIVE-YEAR SURVIVAL	PER CENT	DIED OF MALIGNANCY	PER CENT
I	7	10.6	7	100.0	0	
II	27	40.9	16	59.3	11	40.7
III	13	19.7	4	30.8	9	69.2
IV	12	18.2	5	41.7	7	58.3
V	0		0		0	
(Adeno-acanthoma)						
Unknown	7	10.6	2	28.6	5	71.4
Total	66	100.0	34	51.5	32	48.5

In order to determine the efficiency of the intracavitary radiation, a histologic study of the uterus, tubes, and ovaries was carried out. Multiple sections were obtained and suspicious areas in the uterine wall were even more thoroughly studied. In this group the uteri and adnexa of 67 patients were available for study, all of the patients having received a preoperative course of intracavitary radiation of 4,000 to 4,500 mg. hr. Of this total number, twenty-one, or 64.4 per cent, also received a cycle of deep roentgen therapy of 8,000 r. from four to six weeks following the panhysterectomy.

What are the histologic changes observed following this type of therapy? Nineteen, or 28.5 per cent, of the uteri and adnexa showed no residual malignancy. An analytic survey of the histologic gradings of this group is of interest and here the findings are as follows:

Grade I—occurring in 7 patients.
 Grade II—occurring in 5 patients.
 Grade III—occurring in 2 patients.
 Grade IV—occurring in 1 patient.
 Grade V—Adeno-acanthoma—occurring in 3 patients.
 Unknown—occurring in 1 patient.

In this group there is the same postradiation reaction, namely complete destruction of the malignant growth. It would seem that the maturity or immaturity of the lesion is not of prime importance in the destructive reactions obtained. There are obviously other factors that must be considered, i.e., the size and age of the lesion, the size and conformation of the uterine cavity, the presence of infection, the proper coaptation of radium to the growth and, of the greatest importance, tissue sensitivity.

The histologic gradings of the 67 patients studied now follows:

Grade I—occurred in 15 patients.
 Grade II—occurred in 25 patients.
 Grade III—occurred in 13 patients.
 Grade IV—occurred in 9 patients.
 Grade V—Adeno-acanthoma—occurred in 4 patients.
 Unknown—one not recorded.

From this study it can be seen that in 59 per cent of the specimens investigated the histologic pattern was in the more differentiated grades.

The group in which residual carcinoma is found may be analyzed as follows: of the total number studied there is evidence of malignancy in 48, or 71.7 per cent. Extension into the myometrium is observed in 31, or 64.5 per cent. In 17, or 35.5 per cent, the growth is confined to the endometrium. Metastatic

invasion was found in the tube in four patients whereas the ovary was involved in three. An interesting observation frequently seen is the high incidence of uterine myomas associated with carcinoma of the corpus. In this series 27, or 40.3 per cent, of the uteri contained these benign lesions. Some are of the opinion that the projecting submucosal growth may be an irritant to the endometrium with resulting malignant changes. As is commonly known, there is a high association of hyperplasia of the endometrium concomitant with uterine malignancy. Hyperplasia results from hyperestrinism and some writers have attempted to prove rather unsuccessfully that uterine myomas are produced by the same hormonal stimulus. When one sees atypical borderline areas of hyperplasia where the malignant status is uncertain, one cannot help but be impressed by the possible carcinogenic effect of the overabundant estrogenic factor.

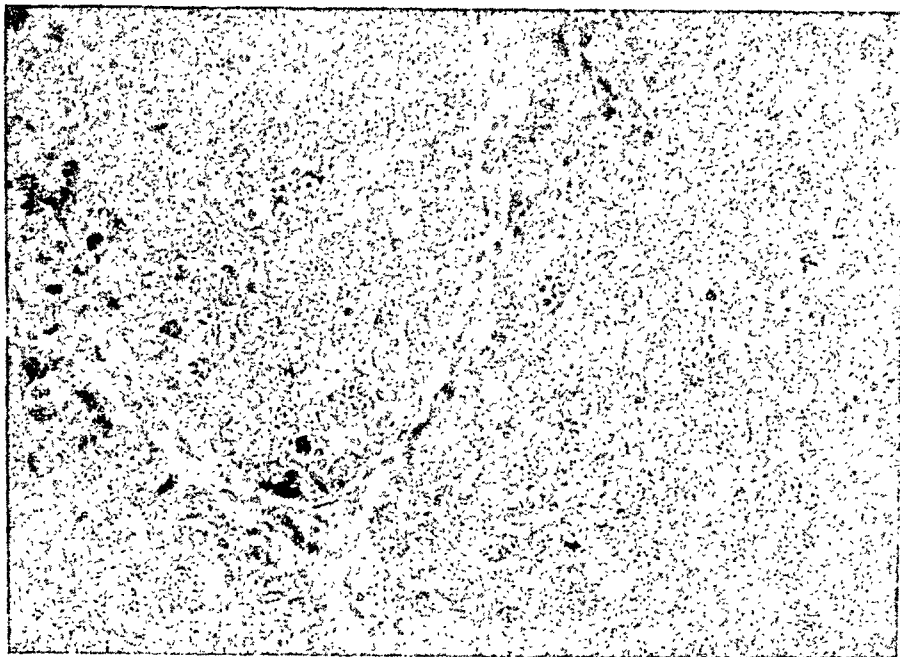


Fig. 1.—Marked anaplasia, Grade IV. Adenocarcinoma curettage.

Variation in Tissue Reaction

On completing a study of the various reactions and results observed in the radiated uteri, one is struck by the marked variation in tissue response. If the growth is confined to the endometrium and there is satisfactory radium application and sensitivity, one can expect a good reaction, as evidenced by absence of viable cells.

This is so well depicted in the case of Mrs. R., aged 43 years, who was observed thirteen years ago for painless vaginal bleeding of about three months' duration. The pelvic examination was normal and a diagnostic curettage was done with the tentative diagnosis of hyperplasia having been made. The tissue obtained was not the amorphous jelly-like material such as that seen with hyperplasia but was of definite form and solid in consistency (Fig. 1). A clinical diagnosis of adenocarcinoma was made and confirmed by histologic study. A markedly anaplastic growth with no cell pattern was seen. Intracavitary radiation was then carried out, the radium being inserted in tandem, and a total dosage of 4,500 mg. hr. was given. Six weeks later a bilateral salpingo-oophorectomy and panhysterectomy were performed. A practical point of value is the clamping of the isthmic portion of the tubes. This precludes the



Fig. 2.—The same tumor as seen in Fig. 1, post radiation, 4,500 mg. hr. Coagulum with complete destruction of the malignant cells.



Fig. 3.—A photomicrograph of the myometrium in the same tumors as seen in Figs. 1 and 2. The endometrium is absent and two normal glands may be seen.

possibility of cells being expelled into the peritoneal cavity during manipulation of the uterus. When the uterus was opened, a circumscribed lesion about 1.5 to 2.0 cm. was found in the region of the right cornu. The tissues were quite pale and the myometrium appeared normal. Microscopic sections showed complete regression of the growth, no viable cells were seen (Fig. 2). The endometrium was absent and in the myometrium two glands were found which showed no evidence of malignancy (Fig. 3). The postoperative convalescence was normal and frequent examinations since then have shown no evidence of disease. If metastasis had occurred, it would most likely have been seen in the vault of the vagina giving the appearance of granulation tissue.

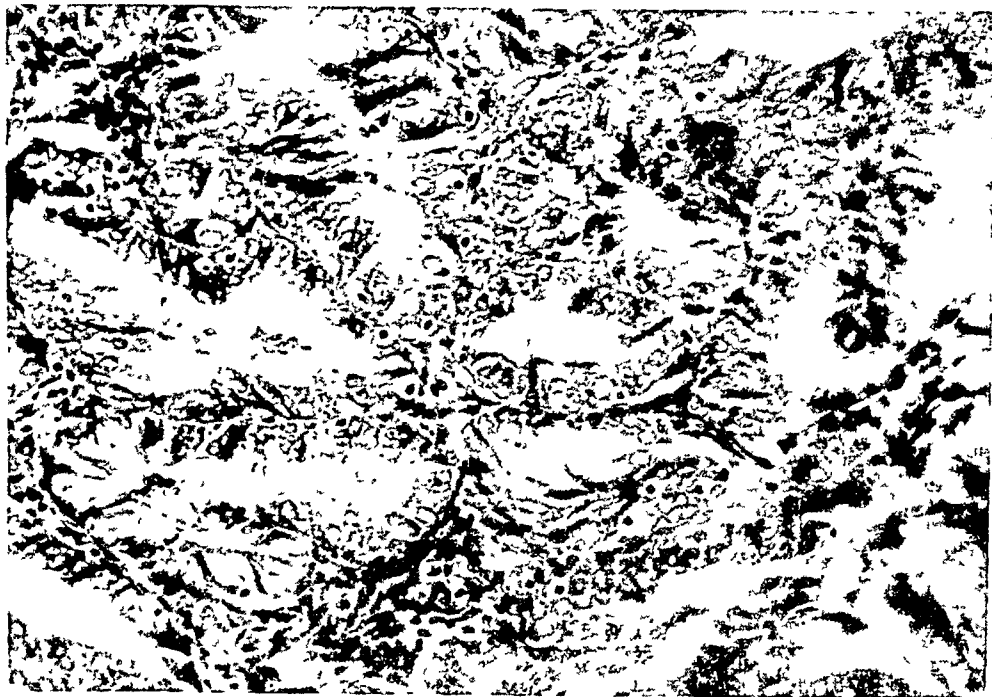


Fig. 4.—Adenocarcinoma, Grade II. Curettage.

Biopsy of any suspicious lesion in the vault is most essential. If radiation is indicated, great care must be exercised to preclude the possibility of fistula formation. In one patient, granulation-like tissue was seen in the vault. This was treated by radiation with a resulting rectovaginal fistula. Unfortunately the surgeon failed to obtain a biopsy prior to the treatment. When one was taken subsequently, no malignancy was found. If it had been known that no malignancy existed, a simple cauterization of the granulation tissue would have sufficed.

In other uteri studied with similar endometrial involvement, varying degrees of cellular devitalization may be seen. These changes range from complete necrosis to cells that show comparatively few changes. These latter, as a rule, are more distant from the focal point of radiation. The common findings, when the growth is in the endometrium, are necrosis, coagulum formation, cellular enlargement with nuclear destruction, fragmentation, and giant-cell formation. Phantom cells also may be seen (Figs. 4 and 5).

The above description is in contrast to that observed when the growth involves the myometrium; here it would seem the cells are somewhat protected by the filtration engendered by the overlying fibromuscular tissue of the uterine wall. These cellular changes are well depicted in Figs. 6 and 7.

A well-known example of tissue selectivity is evidenced in the successful treatment of benign uterine bleeding, which is accomplished by cessation of ovarian activity produced by intracavitary radiation. With us the spaying dosage is 2,000 mg. hr., less than half that used in treating intracavitary carcinoma. The follicular system of the ovary must be extremely sensitive to radiation when one observes its complete dissolution under comparatively small radium exposure at a distance of 4 to 6 cm., always provided the ovary is sufficiently dependent and near the uterine wall. Colwell and Russ³ in their work on *Radium, X-ray and the Living Cell* report an excellent example of selective behavior, i.e., the action of heavy gamma-ray doses of radium upon the kidney.

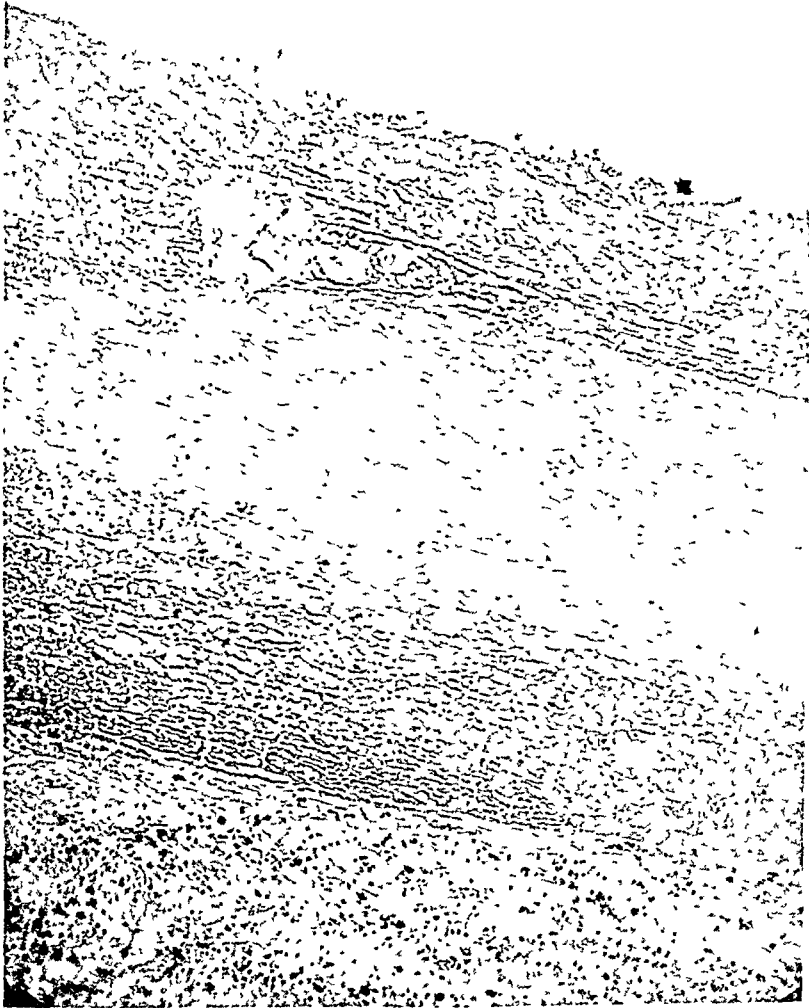


Fig. 5.—The same growth as seen in Fig. 4, post radiation, 4,500 mg. hr. Coagulum with complete destruction of the malignant cells may be seen.

“Here it was possible to observe in one and the same microscopic field that the cells of the convoluted tubules had undergone vacuolation and degeneration while the conducting tubules were apparently but little affected. It is obvious that the amount of radiation to which both types of cells were exposed must have been practically the same.” The explanation of this varying reaction may be dependent on the difference in the embryologic origin of these cells. The

conducting, or collecting, tubules are derived from outbuddings of the ureter which arises from the primary excretory duct, whereas the convoluted tubules are mesenchymal in origin and are of a more specialized nature.⁴



Fig. 6.—Malignant cells seen in the myometrium, post radiation.

Summary and Conclusions

1. The five-year survival rate of 32 patients treated with intracavitary radium and panhysterectomy is 84.4 per cent.
2. The five-year survival rate of 34 patients treated with intracavitary radiation and a cycle of deep roentgen therapy, 8,500 r., is 20.6 per cent.
3. Twenty-one, or 64.0 per cent, of the patients, received an additional post-operative cycle of deep roentgen therapy. The complete therapy in this group consisted of intracavitary radiation, 4,500 mg. hr., panhysterectomy, and a post-operative cycle of deep roentgen therapy, 8,500 r. This added postoperative ray therapy is definitely indicated when extrauterine metastasis is observed. Otherwise it is not obligatory.

4. There was no operative mortality and no untoward sequelae were noted during convalescence.

5. No planned treatment by surgery alone was performed.



Fig. 7.—Polyp, post radiation, showing obliterative endarteritis, malignant cells, and vacuolization.

A Summarized Histologic Study of Radiated Uteri as to Residual Malignancy

1. The uteri and adnexa of 67 patients were available for study.
2. Nineteen, or 28.5 per cent, of the uteri and adnexa showed no residual malignancy.
3. Residual carcinoma was found in 48, or 71.7 per cent.
4. Extension of the growth into the myometrium was noted in 31, or 64.5 per cent, whereas the process was confined to the endometrium in 17, or 35.5 per cent.
5. Tubal involvement was found in four patients and the ovary was affected in three.
6. Uterine myomas were associated with corpus carcinoma in 27 patients, or 40.3 per cent.

From this study the authors are of the opinion that intracavitary radiation by multiple sources, followed by panhysterectomy and bilateral salpingo-oophorectomy is the procedure of choice in the treatment of corpus carcinoma. From the histologic study of the material and from the high observed incidence of residual malignancy the authors feel that panhysterectomy is of the greatest importance. Although residual carcinoma was found in 48, or 71.7 per cent, of the specimens studied, the vast majority of the residual cells shows evidence of radiation reaction even though some of them appeared quite normal.

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622 MEDICAL ARTS BUILDING

Discussion

DR. JOHN L. McKELVEY, Minneapolis, Minn.—There is evidence that the time is ripe for a critical evaluation of some of the conclusions which are presently being drawn in regard to the treatment of adenocarcinoma of the endometrium. Dr. Hundley's study brings some of these problems into focus.

The essayist has raised these problems of the value of x-ray, of intrauterine radium irradiation, and of surgical attack. It is astonishing that students of the subject have come to such diverse conclusions.

One gathers that the author is somewhat skeptical of the effectiveness of x-ray as a method of applying irradiation energy, although he uses it. A considerable part of the American literature would urge preliminary x-ray irradiation as the method of choice. This should be critically examined. It is impossible to tell from the skin dosages which are so often used for reporting just what dosage was obtained at depth. However, a tumor dose at depth of 3,000 to 4,000 tissue roentgens is the maximum that can be given over the usual four-week period. This represents about 1,500 to 2,000 roentgens in terms of biologic effect after recovery rate for comparison with the radium irradiation which is given over only a few days. With combinations of x-ray and radium or with radium alone which supplies about six times this dosage to the uterine cavity, a large proportion of the adenocarcinomas escape destructive effects. Stowe reported on the University of Minnesota material and showed 50 per cent residual tumor after x-ray and radium irradiation. Hundley has shown 71 per cent residual tumor. McLennan reported on a series which was purposefully treated and studied to evaluate the effect of x-ray and concluded that it added nothing to end results. An expensive procedure is added and from four to eight weeks of the duration of life of the tumor is added.

Very large doses of irradiation energy can be given by intrauterine radium in adequate distribution. In contradistinction to x-ray, where only homeopathic doses can be given to what must be considered a relatively radioresistant tumor, the use of the inverse square law to advantage by the use of intrauterine radium will, at least for the surface of the cavity, satisfy the theoretical requirement of 7 to 10 E.S.D. or 7,000 to 10,000 gamma roentgens. But studies as that of Stowe have shown that a maximum of 50 per cent of these irradiated uteri are histologically free of tumor. As such it is useful for those patients in whom surgery cannot be carried out. It is not too clear as to just what we are trying to accomplish by irradiation in those patients who can be treated surgically and we are now collecting a series without preliminary irradiation for comparison.

It is difficult from the reported studies to get any clear idea as to what has really been accomplished. The series are small so that statistical significance is most often lacking. The results of irradiation or of surgery or of both are too often modified by the type of material which is exposed to the specific form of treatment. The further one extends the indications for surgical attack, the smaller the proportion of surgical cures will be produced and vice versa. The question arises as to whether or not an increase in the proportion of patients treated surgically will increase the total recovery rate of the whole group. There is reason to hope that it will, as evidenced by the fairly continuous reporting of 20 per cent recovery rate with irradiation alone and 75 to 80 per cent recovery rate when the surgical attack is used with the customary indications. We have satisfied ourselves that the surgical rate can be increased with reasonable safety. Prior to 1939, 33 per cent were surgically treated. From 1939 to 1942, this rate was doubled. From 1942 to the present, the surgical rate is 75 per cent. The effectiveness of this is still to be proved by a large enough series but it is promising enough to appear to justify agreement with the essayist's statement that "panhysterectomy is of the greatest importance."

DR. CONRAD COLLINS, New Orleans, La.—We would like to comment on the results obtained in Charity Hospital from 1938 to 1943. The reason we surveyed these years is because the new hospital was opened in 1938 and the supply of radium was increased. During this five-year period there were 41 cases treated either by irradiation or irradiation and surgery combined. Counting two untraced patients as dead, in a total of 30 cases treated by irradiation and surgery, there was a five-year survival of 70 per cent. The majority received radium applied in tandem, using three 15 mg. tubes, two applications five to seven days apart, followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. Of the cases treated by irradiation alone, the same dosage of radium was used as well as x-ray, usually 10,000 r. in air; a five-year survival of 29 per cent was obtained. We do not believe that radium and surgery are competitive in treatment of carcinoma of the cervix but that they are complementary and supplementary.

Of the cases shown here, we would like to report a group of 25 cases in which surgery alone was used, in the years 1942 to the present. Surgery did not consist of any extensive operation. Bilateral salpingo-oophorectomy was performed and a generous amount of cuff removed. We do not subscribe to surgery alone. Following surgery in from three months to three years, seven showed recurrence or implantation. Of these, three implantations were in the vaginal cuff, one in the abdominal wound, and three were definite recurrences in the vaginal cuff.

We agree with Dr. Hundley that curettage will not show carcinoma in some cases. However, we believe, in our area at any rate and particularly in our service, that curettage was not used often enough. Occasionally, during postmenopausal bleeding, the patients were operated on without a curettage and I am certain that if they had had a curettage before laparotomy some of these results would have been improved.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Among the many interesting points in this presentation is the statement that over 70 per cent of the uteri that were removed following intracavitary irradiation showed residual cancer. Therefore, much remains to be done in the field of radiation therapy for corpus carcinoma, whether it is to be used as a

preliminary to surgery or as the only therapeutic measure. Paterson states that successful treatment of malignancy depends upon the administration of a tumor lethal dose within the tolerance limits of normal tissues. The problem is one of distributing the sources in such a way as to produce homogeneous radiation throughout a certain volume and then of measuring the dose produced thereby.

In attacking this problem at the Hospital of the University of Pennsylvania, we are experimenting with a slight modification of the Crossen wire technique of intracavitary distribution, which is checked by x-ray examination following each application. The x-ray plates serve three purposes: first, that of detecting possible perforation of the uterus. The accompanying slides shows the only instance of this accident that we have experienced. This perforation was detected within three hours of the radium application and the applicators were removed with no untoward results. Second, the need to see the distribution of the radium sources. In the presence of advanced corpus cancer we believe it is unwise to attempt to administer the desired dose of radiation at one sitting because of the dangers of massive local necrosis and of injury to the contiguous structures. Repeated applications tend to diffuse the ultimate dosage and to avoid what the radiation therapists speak of as "hot spots."

In the case to which I referred the radium was placed fairly evenly throughout the uterine cavity and the attempt to place one or two of the applicators across the top of the fundus was reasonably successful.

Now we reach the most important question: How much irradiation did this uterus receive in terms of tissue dosage? This introduces the third purpose of the x-ray plates: from the two preceding exposures a composite diagram was made to depict the distribution that was obtained in both applications. The measurement and expression of tissue dose in terms of gamma roentgens is an involved problem that is laden with much mathematics and many variables. Our radiation therapists believe, however, that an approximate estimate is feasible and we are indebted to Drs. Eugene Pendergrass and John Freed of the Department of Radiology for their invaluable help and guidance in this work. While we do not know the exact tumor lethal dose of radiation for adenocarcinoma of the uterine corpus, work upon other types of malignancy in other locations suggests that it ranges from six to ten thousand gamma roentgens. The tissue dose approaches that which we believe to be cancerocidal throughout the greater part of the uterine wall. The undertreated areas lie in the external cornual regions and in the cervix—a defect that has been corrected in subsequent applications.

This work is laborious and time consuming but we believe that it has sufficient clinical possibilities to justify its continuation. If it proves to be practical it may lead to the following general procedure: multiple small source intracavitary application by the gynecologist, then transfer to the radiologist for x-ray plates and determination of the length of time that the radium is to remain in place to produce the desired tissue dose throughout the uterus. While this may be a fantastic dream, we cannot escape the thought and the hope that the full usefulness of intracavitary irradiation has not been explored completely. By thinking, not in terms of milligram hours but in terms of tissue dosage to be administered by the even distribution of multiple small sources, it is likely that we can do much to increase the effectiveness of intracavitary irradiation in the treatment of cancer of the uterine corpus.

DR. THOMAS C. PEIGHTAL, New York City.—Dr. Hundley has maintained a splendid record of five-year cures, that is, of the cases that he was able to follow, which surpasses all but one or two of the records in the literature.

Dr. Hundley has noted that an ever-increasing number of women are applying for examination following menstrual irregularity at or near the menopause so that the proportional incidence of adenocarcinoma as compared with cervix carcinoma in his clinic has risen to a ratio of 1 to 5. A majority of his cases occurred in multiparas (64.6 per cent); 85 per cent were at or after the menopause, and the average age was 55.9 years, only 36.3 per cent being over 60 years. The low incidence of corpus cancer in the Negro race is

interesting (117 whites to 6 Negro women). Dr. Hundley notes that favorable prognosis varies according to the size of the cancer-bearing uterus, to which all must agree.

For his ideal treatment of the good-risk patient, Dr. Hundley irradiates the fundal cavity with multiple source applicators and his dosage of 4,000 to 4,500 mg. hr. of irradiation seems adequate. This is followed by panhysterectomy with bilateral salpingo-oophorectomy six weeks later and in the majority of cases (21 out of 32) a pelvic cycle of roentgen therapy for a total of 8,000 r. was given four to six weeks after laparotomy. In this group he has obtained the excellent result of 84.4 per cent five-year cures. This is a determinate percentage based on just the total cases followed (32 in number).

For the poor-risk group (34 in number), Dr. Hundley uses 4,000 to 4,500 mg. hr. of intracavitary irradiation followed, or in some instances preceded, by roentgen therapy of 8,500 r. and in this group he has obtained only 20.6 per cent five-year survivals, but it must be emphasized that these were all poor-risk patients.

Dr. Hundley has shown us the percentage of five-year survivals according to the various pathologic gradings. Among these, 52 per cent of his cases were in Grades I and II and in these he obtained 68 per cent five-year survivals by all methods of treatment. One wishes that he had noted his end results on the basis of pathologic grading for each of his two types of treatment, i.e., irradiation alone and irradiation plus surgery.

In the histologic study of uteri removed, it is to be noted that in 19 (28.5 per cent) there was no residual malignancy after the preliminary irradiation. Since these favorable results were found in all pathologic grades, he feels that other factors such as clinical stage of disease may be the more important factor in growth eradication by intra-cavitary irradiation. In the 71.1 per cent showing residual cancer after irradiation, inability to obtain accurate application of the multiple source capsules, because of the presence of myomas or extensive myometrial involvement, seems to have been the chief cause of failure. A splendid histologic study of tissue response for growth, both in the endometrium and myometrium, has been undertaken and is carefully evaluated.

We have ready for publication a report of 157 cases of carcinoma of the endometrium from the Roosevelt Hospital. The average age incidence has been 56 years, only 18 per cent have occurred in the Negro race, and 58 per cent in multiparas. The average age at menopause has been 49 years and 36 per cent had myomas.

It is obvious from our own experience, when analyzed from the standpoint of stage of lesion and grade of malignancy, that preoperative irradiation plus hysterectomy offers no advantage over hysterectomy alone in *early* lesions or in *low* histologic grade; and very little advantage in *advanced* lesions or *high* histologic grades. In support of this it is interesting to show a few slides of composite results from various clinics.

As the risk of being declared a radical we submit the question, "Can we go above 80 per cent five-year survivals by present methods of treatment?" Probably not because of nodal involvement and distant metastases.

We submit therefore that in good-risk patients it is likely that our best results in the future will be obtained from a more extensive hysterectomy, i.e., a wider excision of parametria with, where possible without undue risk, a lymphatic node dissection, particularly where nodes are obviously involved. Since the average age incidence of these patients is 56 years, more than is usually supposed of them are good-risk patients. True, many are obese, but for them we can envisage among the proponents of more radical surgery in corpus carcinoma even a three-stage operation of 1. wide hysterectomy; 2. several weeks later, an extraperitoneal lymph-node dissection by the inguinal approach on one side as described by Nathanson, Parrous, and Meigs; and 3. still later, a similar node dissection of the other side. Is it not possible that our best results may eventually come by such a procedure?

However, Dr. Hundley has obtained a very high percentage of 5-year survivals (84.4 per cent) by his method of treatment—radium plus hysterectomy in good-risk patients. This compares favorably with Dr. Norman Miller's series of 96 cases treated by preoperative roentgen therapy plus hysterectomy with a 77 per cent five-year survival, and more than

favorably with five-year results either from surgery alone, or from radium, x-ray, and surgery combined in all other clinics. Therefore, Dr. Hundley is to be congratulated for a most excellent paper and for his splendid results.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—I am still able to report a 100 per cent follow-up of all of the patients with fundal carcinoma seen in the Division of Gynecology, Department of Obstetrics and Gynecology, at Jefferson Medical College and Hospital since 1921, 207 in number.

In the case of the group of patients in whom radium, and radium alone, was used prior to surgery, our five-year and longer surgical figure is 85.2 per cent. This applies to 27 patients eligible for five-year statistics. In addition are 29 more patients, of whom 28 have survived from one to four years or a bit longer. Neither has there been a surgical mortality among these 56 patients. Thus, we have found from our experience that preoperative radium has added a great deal to our immediate and long-term survival record.

I will not go into details about this "planned technique" and its application, for our procedure has been published repeatedly in the past. I have never believed that the preliminary application of radium destroys all of the cancer, but it certainly attenuates its vigor and renders subsequent surgery safer and more effective, especially with respect to recurrence in the vaginal vault scar. This was not true of the methods used in the earlier days. I can subscribe substantially to many of the points that Dr. Hundley has brought out.

DR. GEORGE W. KOSMAK, New York City.—I desire to refer to a matter that may not bear directly on this discussion but which seems to me of considerable importance. As a result of the nation-wide propaganda for the early detection of cancer, there have been opened in many places in this country so-called "cancer detection centers." It must be acknowledged that the early diagnosis is one of the most important topics that should be considered in the attempt to eradicate this disease. It seems to me, however, that it would be desirable if organizations with authority, such as the American Gynecological Society, would develop certain standards of practice for the so-called "detection centers." It has become a very popular movement in many counties over the country to open these centers. Now my hesitancy about the value of some of these centers is based on a report that I received for publication a year ago in the JOURNAL, emanating from a contraceptive clinic in the neighborhood of New York City. As you know, this organization has been very desirous of exploiting the fact that they are able to detect a great many gynecologic conditions in giving contraceptive advice. To quote one result from this clinic: the author of the paper claimed that, within a certain period 3,000 patients had been examined and in only four cases were any lesions of the cervix detected that merited reference to a physician. There is something at fault there when we have such results from what might be expected from reliable observations. I am sure that every one who has practiced gynecology will subscribe to the fact that in 3000 cases examined there would be more than four with lesions that needed further investigation. I hope as a result of the papers and discussions presented some action will be taken through this organization or through the American Cancer Society to establish certain standards of examination for these various cancer detection centers.

DR. HUNDLEY (Closing).—I have nothing further of significance to offer. There are many pros and cons concerning this problem which we could debate ad infinitum. However, as the hour grows late and there are still several papers to be presented I will not detain you with irrelevant remarks.

Dr. McKelvey is to be congratulated on his splendid results with surgery alone. We feel that panhysterectomy can be performed with a high five-year survival rate provided that the microscopic pattern of the growth is of the mature type; we also feel that the operative results obtained are poor when the growth is of the anaplastic group.

In closing, I wish to state that I still feel that the combination treatment, i.e., intracavitary radiation followed by panhysterectomy, is the method of choice in the treatment of adenocarcinoma of the body of the uterus for by this method we have obtained an 84.4 per cent five-year survival rate.

FACTS PERTINENT TO A RATIONAL CONCEPT OF ABRUPTIO PLACENTAE*

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IT IS the purpose of this paper to restate facts which have heretofore admittedly supported a toxemic origin of abruptio placentae and to present additional facts strengthening this viewpoint.

The following clinical and pathologic evidences indicate that abruptio placentae is a manifestation of toxemia of pregnancy and is a phenomenon which may occur in any case of severe toxemia and interrupt the pregnancy before the convulsive stage is reached:

1. *The Frequent Occurrence of Symptoms and Findings of Toxemia Preceding Abruptio Placentae.*—

A majority of the cases of abruptio placentae shows typical clinical evidences of toxemia some days or weeks before hemorrhage and separation of the placenta terminate the pregnancy, i.e., increasing edema, headache, rising blood pressure, increasing albuminuria, arteriolar spasms in the retinas and increasing blood uric acid. The severity of the abruptio parallels not only the co-existence but particularly the severity of the toxemia.

Portes found an associated toxemia in 91.3 per cent of the cases of abruptio placentae in Couvelaire's Clinic.¹ Dieckmann¹ found that 69 per cent of cases of abruptio placentae at the Chicago Lying-in Hospital had associated toxemia. In a former study² evidence of toxemia of pregnancy was found in 33 of 61 cases analyzed. A study of the literature reveals many analyses emphasizing this association.^{13, 14}

Due to the fact, however, that a variable percentage of cases, particularly of the fulminating type, fails to show clinical evidences of toxemia, there has been no unqualified acceptance of a toxemic origin of abruptio placentae. Evidence which establishes a toxemic basis in this group of apparent exceptions will be presented later in discussing the pathology of the condition.

2. *Simultaneous Occurrence of Eclampsia and Abruptio Placentae.*—

Occasionally, toxemic patients are affected by abruptio placentae and eclampsia simultaneously, as in Cases 28 and 42, in the present series. This indicates that toxemia is probably the common etiological factor. Pathologic evidence leads further support to this view.

Furthermore, it is not uncommon to find a subclinical mild degree of abruptio placentae in the placentas of patients who have eclampsia.

3. *Similarity of Necropsy Findings in Eclampsia and Abruptio Placentae.*—

The similarity of the pathologic findings in the liver, kidneys, brain, and other vital organs indicates an etiological agent common to both conditions, but with a greater predilection to damaging effects on the mechanism of blood coagulation, hemorrhagic manifestations, and vascular damage, in abruptio placentae.

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

Necropsy: C. R., Hospital No. 304650, aged 32 years, gravida ii, para i; history of orthopnea and nocturnal dyspnea past several years; at seventh month of present pregnancy had sudden hemorrhage, estimated one pint; had developed edema and headache two days preceding; blood pressure 200/160, heart enlarged, moderately severe vascular disease, no spasms, numerous flameshaped hemorrhages in retina; albumin 2 plus; uterus tense, fetal heart not heard; diagnosis, abruptio placentae. Sedation and supportive treatment; spontaneous onset of labor and delivery, 1,640 Gm. slightly macerated fetus; 500 c.c. blood and old clots followed placenta, which showed indented area of premature separation but unfortunately not examined for infarction. Delivery followed by increasing orthopnea and dyspnea; one transfusion, continuous oxygen, rapid digitalization; blood pressure 220/160, pulse 128, development of pulmonary edema; sudden death in cardiac failure several hours later. Necropsy performed. Summary of findings: "Histologically, this patient showed the lesions diagnostic of toxemia of pregnancy"; arteriolitis with formation of fibrin thrombi in damaged arterioles, seen in kidney (thrombosis of afferent arterioles and infarction of glomeruli), also in terminal branches of hepatic artery and sinusoids of liver, and in pulmonary arterioles.

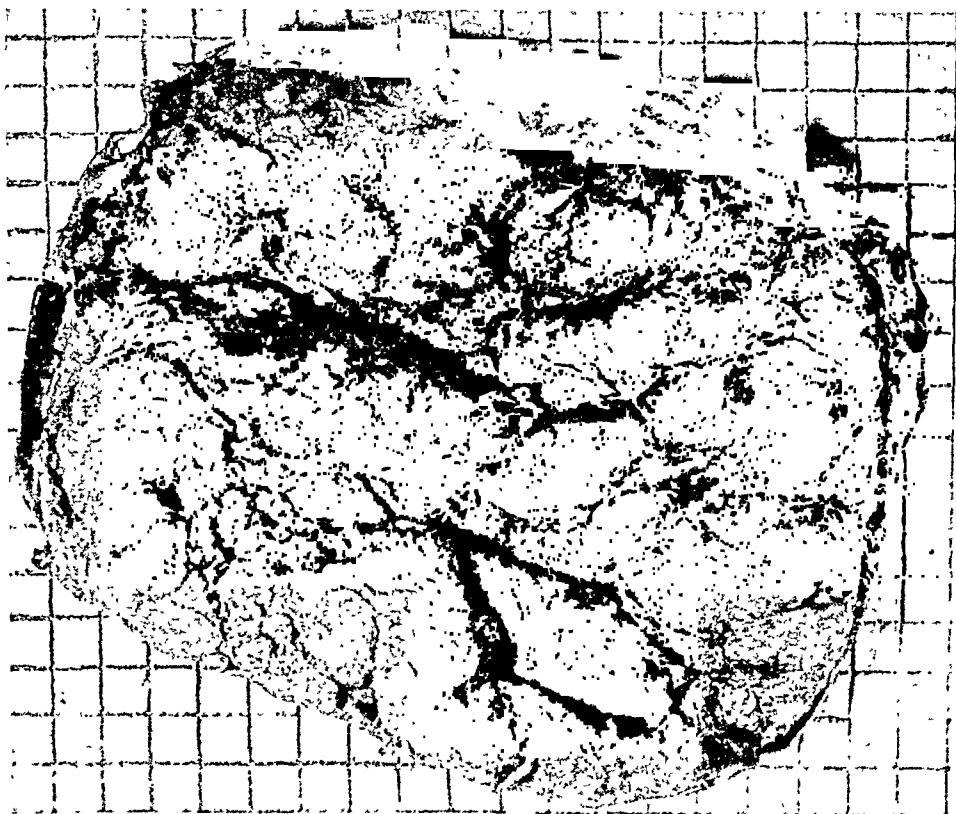


Fig. 1.—Abruptio placentae, Case 43; upper two-thirds dark due to acute hemorrhagic infarction; lower third normal.

The above facts constitute strong circumstantial evidence but have apparently not been regarded as sufficient to indict toxemia as the cause of abruptio placentae.

The following additional evidence establishing a specific pathology in the placentas, common to both eclampsia and abruptio placentae, should justify acceptance of toxemia of pregnancy as the etiological factor common to both.

4. *The Consistent Occurrence of Acute or Subacute Hemorrhagic Placental Infarcts in All Cases of Abruption Placentae and Eclampsia, Identical in Both Gross and Microscopic Appearance.*—

Placentas from consecutive cases of abruption and eclampsia from several of the local hospitals were saved over a period of a year. The following is a summary of the clinical and placental findings in a series of fifty placentas examined:*

- 20 cases of abruption placentae
- 6 cases of eclampsia
- 2 cases of abruption and eclampsia
- 4 cases of severe or pre-eclamptic toxemia
- 18 cases of normal pregnancy, included for comparative placental diagnosis.

50 total number of cases. No maternal mortality.

20 *Cases of Abruption Placentae:*

- 15 or 75 per cent showed vascular disease (retinal examination).
- 12 showed shock, mild to severe.
- 9 had severe hemorrhage (estimated 800 to 1,200 c.c.).
- 11 had moderate hemorrhage (estimated 500 to 800 c.c.).
- 12 had tense uterus (eight not mentioned).
- 7 had unfavorable cervix (1 to 3 cm. in length) but were successfully induced by artificial rupture of membranes.
- 19 were fulminating.
- 9 babies stillborn; 3 neonatal deaths; one fetus aborted at 4½ months with associated abruption; 7 babies survived. Fetal mortality 60 per cent.
- 14 had one to six transfusions. Average of 3.6 transfusions each.
- 6 did not require transfusion.
- 20 (100 per cent) showed well-defined early "E" infarction, which agreed with clinical diagnosis of toxemia.
- 20 (100 per cent) delivered spontaneously, following either spontaneous labor or successful induction.

6 *Cases of Eclampsia:*

- 1 showed vascular disease.
- 2 were fulminating.
- 6 (100 per cent) showed well-defined early "E" or "D" infarction which agreed with the clinical diagnosis.
- 1 stillbirth; 4 babies survived (1 baby chart missing). Fetal mortality 20 per cent.
- 6 (100 per cent) had spontaneous delivery after induction of normal labor.

2 *Cases of Abruption Placentae and Eclampsia Combined:*

- 2 cases showed vascular disease.
- 1 case showed shock.
- 2 cases had moderate degree of hemorrhage.
- 1 case had tense uterus.
- 1 case had unfavorable cervix.
- 1 neonatal death; 1 baby survived.
- 2 cases showed well-defined early "E" infarction which agreed with clinical diagnosis.
- 2 cases delivered spontaneously.

4 *Cases of Severe or Pre-eclamptic Toxemia:*

- 4 showed well-defined "E" infarction (2 early "E," 2 late "E").
- 4 had spontaneous delivery.

18 *Cases of Normal Pregnancy (Included for Comparison of Placental Findings):*

- No cases of vascular disease, shock, hemorrhage or fetal mortality.
- 6 cases showed no recognizable area of infarction.
- 8 cases showed questionable "E" infarction, in gross examination.
- 4 cases showed well-defined early "E" infarction, although clinically normal.

Summarizing these results, it was found that if the patient had eclampsia, abruption, severe or pre-eclamptic toxemia, well-defined early or late "E" infarction of the placenta was always present (32 cases—100 per cent).

*The details of the clinical and placental findings in each case are omitted here for the sake of brevity, but are included in the reprints.

Nineteen of the abruptio cases and two of the eclamptic cases in this series, were so fulminating, that preceding clinical symptoms and findings were absent or mild, yet unmistakable infarction was present in the placentas in all cases and indicated an associated severe toxemia.

If the patient was clinically normal throughout pregnancy, or at the last prenatal visit, within two weeks of the onset of labor, six of the eighteen cases (33 per cent) showed no recognizable infarction.

The total number of toxic and normal cases in agreement with the placental findings was 76 per cent.



Fig. 2.—Strip from placenta of Fig. 1; sharp line of demarcation between confluent dark early "E" hemorrhagic infarction involving two-thirds of the placenta (to left), and the lighter normal placenta (to right).



Fig. 3.—Abruptio placentae, Case 7; placental strip showing both confluent and isolated early "E" hemorrhagic infarction.

The four well-defined early "E" infarctions in clinically normal cases, may have been early infarctions, too early for recognizable clinical effect.

The eight questionable "E" infarctions in clinically normal cases may have been due to temporary partial obstruction by sphincters of the placental veins, just before or early in labor. Comment on these will be found in the discussion.

5. In Cases of Abruptio Which Occur During the Course of Gradually Increasing Toxemia, the Location, Appearance, and Consistency of the Blood Clot Indicate That the Initial Bleeding Takes Place at the Site of and Adjoining a Recent Hemorrhagic Infarction of the Placenta (Fig. 6).—

The maternal blood extravasates first at this point, as shown by the greater indentation and compression of the placenta and the greater firmness and age of the clot at this site. The prognosis for the baby is therefore better if the infarction is nearer the margin of the placenta. (Case 15,42 Fig. 6.)

Kellogg and Hertig³ are of the opinion that a pathologic process apparently resembling cholesterol-vascular change, affects the intima and lining of the maternal arteries as they reach the placental site and causes spontaneous rupture, extravasation of maternal blood, and abruptio placentae. Reasoning from the

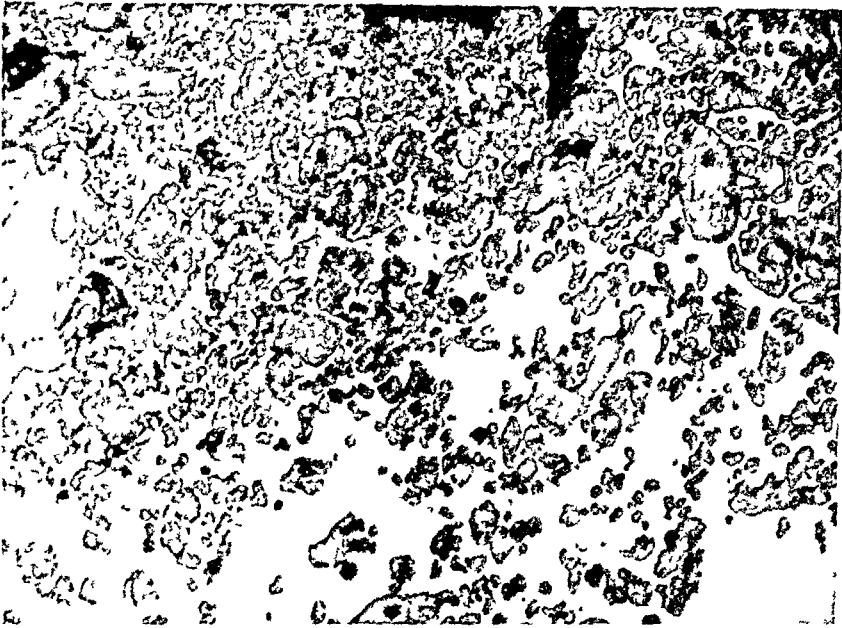


Fig. 4.—Abruptio placentae, Case 43, Fig. 2; low-power magnification at junction of acute hemorrhagic early "E" infarction above, and normal tissue below. The infarcted tissue above shows enlarged, crowded, congested villi; the normal tissue below shows loosely spaced, small, noncongested villi.



Fig. 5.—Abruptio placentae, Case 43; higher magnification of acute hemorrhagic early "E" infarcted tissue showing enlarged crowded villi, early necrosis and greatly distended villous vessels.

effect of similar change seen in the coronary arteries, it would seem that thrombosis, rather than rupture and hemorrhage, would be the expected result.

The fact that a more advanced stage of necrosis in the infarcted placental tissue, type "D" (Fig. 6), is often seen, indicates an older process than the more recent blood clot adjoining and compressing the infarction and favors

irritation around the silver wire. All medication was discontinued at this time. On October 9, silver wires were removed and the wound was healing by primary union. Patient was discharged the following day (fifteen days postoperative) in good condition. As seen from the case history, except for a slight chill and fever immediately following the last (fifteenth) transfusion, there were no other signs of a hemolytic or pyrogenic reaction.

We should like to consider the amount of sodium citrate injected. Lewisohn, after experimentation on dogs in 1915, concluded that 15 Gm. to a man would be fatal, but since this pioneer work, his dosage limit has often been safely exceeded.¹¹ There have been reported as much as 5,600 c.c. of citrated blood over a period of forty-eight hours. Our patient, a 52 Kg (115 pound) woman, received 7,500 c.c. of citrated blood in a six hour period with little or no reaction. The exact action of sodium citrate is not known but it is believed that the sodium citrate forms a complex soluble salt (with calcium) which liberates very few calcium ions. Bruneau and Graham¹¹ have shown the toxic effects of sodium citrate to vary with the dosage and repetition of a certain dose, with the rate of administration, with different animal species, and even with different members of the species. To duplicate their experimental conditions, a man weighing 70 Kg. (154 pounds) would have to be given 6,300 c.c. of blood containing 0.6 per cent citrate within a few hours before a fatal outcome could be expected. This is equivalent to 37.8 Gm. of citrate. In each 500 c.c. bottle given to our patient there was 75 c.c. of anticoagulant containing 2.2 per cent sodium citrate and 0.8 per cent citric acid. Ultimate concentration was 0.33 per cent sodium citrate and 0.12 per cent citric acid. Therefore, 7,500 c.c. of whole blood contained 24.75 Gm. of sodium citrate and 9 Gm. of citric acid.

It is interesting to note that the blood loss in this case was greater than 100 per cent. According to the Ashby method,³ one bottle of blood forty-eight hours after administration corresponds to a cell volume of 2.8 per cent (350,000 red blood cells per cubic millimeter). The patient's count at forty-eight hours showed:

Total red cell count	3,850,000
Transfused red cell count	5,250,000
Cell volume of patient	38 per cent
Allowance for 15 bottles of blood	42 per cent

Summary

1. Patient received 7,500 c.c. of whole blood in a six-hour period which attests the value of an efficiently functioning blood bank.
2. Rapidity of administration can be easily accomplished by a syringe and a three-way stopcock.
3. Group O Rh-positive blood has a low titer (1-200 or less) of Anti-A and/or anti-B agglutinins and hemolysins.
4. Citrate has low toxicity, a 52 Kg. woman tolerating 33.75 Gm.
5. Active and proper therapy aids in the establishment and maintenance of kidney function post transfusion.

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pound, 11 ounce baby girl lived for four hours and post mortem revealed atelectasis with no other abnormalities except facial deformity. Suter and Wichser¹² found that 38.7 per cent of living viable babies in extrauterine pregnancies were deformed and 24.3 per cent of the babies died before the eighth day. They quoted Winckel as stating that 75 per cent of all deformed children had abnormalities of the head. Following operation, the patient's pulse which had been unobtainable became discernible but was too rapid and weak to be counted. Blood pressure was 70/50 at this time. Nasal oxygen was started, and blood and plasma were given under syringe pressure through cutdowns in both arms. Despite the eight bottles of whole blood (the first three, group A crossmatched, the remainder group O unmatched) and 750 c.c. of plasma, the patient again went into deep shock. Blood pressure and pulse were unobtainable, red blood cells 3.05 millions, hemoglobin 10.7 Gm. (73 per cent), hematocrit 32. The abdomen was distended, tense, and dull to percussion. It was felt that the patient was hemorrhaging internally and the abdomen was reopened through the old incision at 2:45 P.M. (two and one-half hours after the first closure) under light gas-oxygen anesthesia. Approximately 2,000 c.c. of blood and clots were removed from the peritoneal cavity and a bleeding area the size of a dime was found on the right posterior margin of the placenta. This area was the site of active hemorrhage. The placenta and membranes were delivered through the abdominal wound and, as they were not attached to the intestines, clamps were placed across the omental attachment above, and the right Fallopian tube below. These attachments were cut and sutured. The raw area in the right gutter was packed with Oxycel gauze, the abdomen closed with through-and-through silver wire, and the skin with interrupted black silk sutures. During this procedure and immediately postoperatively, an additional seven bottles of whole blood (six, group O unmatched, one, group A crossmatched) and 500 c.c. of plasma were administered. Patient had a slight chill at this time. At 6:00 P.M., the blood pressure was 120/80, pulse 140, temperature 103.6° F., red blood cells 3.4 millions, hemoglobin 15.8 Gm. (106 per cent), hematocrit 47. The patient was taken to her room and placed in an oxygen tent and a Miller-Abbott tube inserted. Penicillin, 75,000 units every three hours and a course of Prostigmine were ordered. During the next twenty-four hours, sixteen ampules of sodium lactate were administered. The latter was given in glucose, in distilled water, and in normal saline. She was also given Parenamine, and vitamins at the same time. Urinary output during the first seven postoperative hours was 1,500+ c.c. (via retention catheter); the urine was alkaline, containing 5 to 10 red blood cells per high power field.

	2ND DAY	3RD DAY	5TH DAY	7TH DAY	11TH DAY	12TH DAY
Output (c.c.)	4,140+	2,950	1,200+			
Intake (c.c.)	5,000	3,260	3,320			
Red blood cells	4.85	3.85	4.15			4.7
Hemoglobin	14(97%)	11.3(77%)	12.5(86%)		16(108%)	14(96%)
Hematocrit	40	38	40		47	
Urea	14	15	18	24		
Uric acid	2.4			3.6		
Chlorides	560	610		568		
Total protein	5.0			5.8	7.7	7.2
Carbon dioxide	52.3			37.4		
Icterus index	2.5					
V.D.B.	0					

The patient was given fluids (with Miller-Abbott tube clamped) on morning of September 27 (40 hours postoperative), which she retained. The Miller-Abbott tube was withdrawn that same morning. Blood pressure maintained at 115/70 and pulse came down to 80 on September 26. The temperature returned to normal on September 27. Oxygen was stopped at this time and the patient placed on a soft diet with no distention present. Aside from a fear of impending death, the patient's convalescence was entirely uneventful, and she was allowed out of bed on September 30 (sixth postoperative day). On October 2, the black silk sutures were removed and the wound looked clean at that time although there was slight

Red blood cells 2.8, hemoglobin 39 per cent, white blood cells 15,600. Five hundred cubic centimeters of plasma and 500 c.c. of whole diluted blood were started in both arms. During surgery another 500 c.c. of blood were given.

When the abdomen was opened under ether and nitrous oxide anesthesia, the peritoneal cavity was filled with fresh and old blood, and much soft, mushy, brainlike material. The uterus was the size of six and one-half to seven months' gestation, and intact. A large, ruptured, left ovarian cyst was delivered with frayed margins. The right ovary contained a corpus luteum of pregnancy. The impression was that of a unilateral, ruptured, malignant ovarian tumor. Owing to the patient's critical condition, only a salpingo-oophorectomy was done, and the abdomen was closed immediately.

Pathology report by Alex B. Ragins, M.D. "Specimen of ovary presented a morcellated appearance, the largest fragment measuring 15 by 9 by 2 centimeters. The free surface was light purplish-gray, smooth, and appeared to be part of a cyst filled with soft, putty-like material. Microscopic section of ovary revealed a very anaplastic undifferentiated carcinoma of the ovary with a tendency to form glandlike structures."

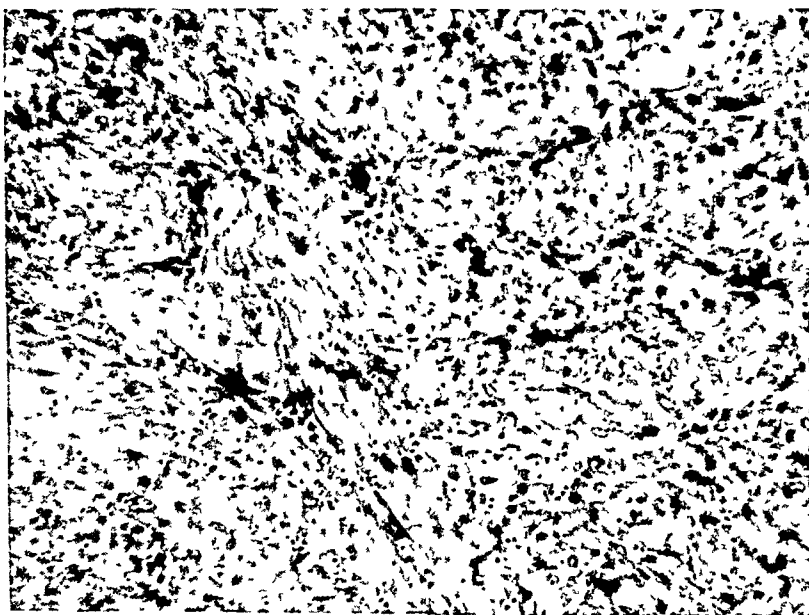


Fig. 1.—Ovarian tissue revealing a very anaplastic undifferentiated carcinoma, with tendency to form glandlike structures

Her postoperative course was uneventful. Ten days later, x-ray therapy was started. It was decided to give the patient a full course of therapy before further surgery was contemplated. Twenty-five days postoperatively, she went into labor and passed a macerated fetus of about six and one-half months' development. The patient received 250 r. (in air) through eight portals, for a total of 3240 r. per portal. Subsequently she refused further surgery and hospitalization. We had planned to do a total hysterectomy and a right salpingo-oophorectomy. According to the relatives, the patient is now in Jackson, Mississippi, and is reported to feel perfectly well.

Summary

1. Primary ovarian malignancy complicating pregnancy is uncommon.
2. Nineteen authentic cases are reported in the literature; of these nine are sarcomas, the remainder being carcinomas.
3. That herewith reported is the only case of ruptured ovarian malignancy associated with pregnancy.

SPONTANEOUS RUPTURE OF A PRIMARY CARCINOMA OF THE OVARY COMPLICATING PREGNANCY

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PRIMARY malignancy of the ovary complicating pregnancy is uncommon. Case reports are conspicuously few in the literature. It has been stated by Szathmary⁹ that 5 to 7 per cent of ovarian tumors associated with pregnancy are malignant. Traut and Kuder reported 53 ovarian tumors in 2,300 deliveries. Two were malignant; an incidence of 3.7 per cent.¹¹ At the Cook County Hospital, this is the only recorded proved case since 1932.

In 1942 Brossert presented fifteen authentic cases.¹² His summary failed to include cases reported by Danforth and Greenhill.^{7, 8} In 1933, Van Szathmary stated that he had found thirty-nine cases in world literature, of which seven were sarcomas and thirty-two were carcinomas.⁹ Most of these cases, however, were obtained from various clinical tabulations of ovarian tumors. In most instances authenticity of the malignancies, in the presence of pregnancy, was not verified by microscopic study.

We wish to present a case, and to add to the official list the following cases: Wells (1882), Casati (1883), and Murphy (1895), as revealed by Swan in 1898.¹ We feel that the case of Hempel, which was evidently a bilateral Krukenberg ovarian tumor secondary to carcinoma of the stomach, should not be included in the list of primary ovarian malignancy complicating pregnancy. This brings the total number of authentic reports to nineteen.

Case Report

B. H., a 24-year-old Negro woman, gravida iii, para ii, was admitted to Cook County Hospital on July 10, 1947, in the service of Dr. Daro. Her last period had occurred on Oct. 3, 1946. She attended prenatal clinics of the Infant Welfare Society. Their initial examination on Feb. 2, 1947, showed no pelvic pathology.

Her complaints on admission were: abdominal cramps for two days, fainting and weakness for the past five hours. Pregnancy had been uneventful until two days prior to admission, when she noted the onset of lower abdominal discomfort. The pain was intermittent and mild at first, but became more frequent, severe, and diffuse. About five hours prior to admission, the pain suddenly became sharp, and the patient felt weak and faint. Her abdomen began to feel "bloated." She was seen by physicians from the Chicago Maternity Center. They found her in shock, with a blood pressure of 70/40, gave plasma and stimulants, and sent her to Cook County Hospital.

Physical examination on entrance revealed an acutely ill Negro woman, manifesting mild dyspnea and beads of perspiration on her forehead. Her blood pressure was 90/60, temperature 97° F., and respirations 28. The skin was cold and clammy; the conjunctivae and oral mucosa were pale. Lungs were clear and resonant. Abdomen was distended, tense, and tympanitic. Liver, kidney, and spleen were not palpable. Peristaltic sounds were absent. Fundus of the uterus extended two finger breadths above the umbilicus. Corpus felt firm, tense, and somewhat tender to palpation. Fetal sounds were not made out. External genitals were negative, with no evidence of fresh or old blood. Clinical impression was: abruptio placenta, or possible ruptured uterus. Urine was negative for sugar, acetone, and albumin.

*Presented before the Chicago Gynecological Society, Feb. 20, 1948.

DYSGERMINOMA OVARIII*

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THE following two cases were seen with Dr. E. L. McGill and Dr. J. L. Hagan, respectively, at the St. Francis Hospital in Evanston, Ill., and it is with their courteous consent that this report is made. Both cases are of dysgerminoma ovarii, or, as they are sometimes called, seminomas. In each case, repeated strongly positive Aschheim-Zondek and/or Friedman tests were obtained. The majority of the literature, including textbooks dealing with dysgerminoma ovarii, describe these tumors as incapable of producing demonstrable changes in hormone balance.

The first case was that of a 23-year-old nun, first seen in August, 1939. She complained of having had intermittent left abdominal pain for six years, and then for the past year of an almost constant aching pain in her left abdomen. She had noticed her abdomen becoming larger. One year previous to admission she had had amenorrhea for four months; since then menses had been characterized only by irregularity. The only significant physical finding was a symmetrical firm abdominal tumor rising from the pelvis to 5 cm. above the umbilicus. There were no breast changes. X-rays of the abdomen were negative for fetal structures. The Aschheim-Zondek test was strongly positive on three occasions prior to operation. At the operation a grey-pink, rubbery, smooth tumor replacing the right ovary was removed. Its greatest diameters were 19 by 22 by 13 cm., and its weight 2.1 kilograms. The rest of the pelvis was apparently normal, and the recovery was uneventful. Fourteen days postoperatively an Aschheim-Zondek test was negative, and in March, 1947, seven and one-half years after surgery, the patient was reported to be alive and well.

The second case was similar and first seen in September, 1946. The patient was 23 years old, unmarried, and had always been in good health. She had bled vaginally for three weeks in May, 1946, and had been told that she was very anemic. In June, 1946, she had an apparently normal menstrual period, then amenorrhea for thirteen weeks preceding admission. For about six months she had noticed that her lower abdomen was enlarging, and the only significant finding on physical examination was a symmetrical midline, nontender, tumor mass extending out of the pelvis to 3 cm. above the umbilicus. There were no breast changes, and x-rays of the abdomen were negative for fetal structures. Repeated Aschheim-Zondek tests were strongly positive in two laboratories, and Friedman tests were likewise positive in a third laboratory. At operation a grayish-purple left ovarian tumor of rubbery consistency measuring 18 by 20 by 14 cm. was removed. The other pelvic structures appeared and felt normal. Cut sections of the tumor were gray to gray-pink, with a few streaks and spots of yellow. There was only one cystic area, 2½ cm. in diameter. The patient's recovery was uneventful. Aschheim-Zondek tests done on the tenth and thirtieth day postoperatively were both negative, and a Friedman test done on the fourteenth postoperative day was negative. To date the patient is in good health.

In summary, then, two cases of dysgerminoma ovarii were associated with strongly positive "pregnancy tests;" these reactions became negative after the ovarian tumors were removed. The incidence of malignancy in these tumors has been reported as high as 30 per cent. Both of these patients are living and well, one more than seven and one-half years after surgery.

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4. Ruptured ovarian malignancy may simulate abruptio placenta, ruptured uterus, and the other conditions associated with pregnancy causing an acute abdomen.

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The febrile reaction during the early part of the illness was marked. The temperature rose steadily to 106.2° F. on the second postpartum day. With improvement which followed by the third day it remitted to 103.4° F. and gradually fell to 101° F. on the sixth day, becoming normal and remaining flat the remainder of her postpartum course. Pulse and respiration followed closely changes in temperature.

The spinal fluid was removed under increased pressure. It appeared cloudy with 4,048 cells, 95 per cent polymorphonuclear leucocytes and 5 per cent lymphocytes with 91 mg. per cent sugar. A repeat examination of the spinal fluid at the end of the first postpartum day still showed increased pressure and cloudiness with 5,900 cells, 95 per cent polymorphonuclear leucocytes, 5 per cent lymphocytes with less than 10 mg. per cent sugar and 191 mg. per cent total proteins.

Smears and cultures remained negative. No bacterial agent was recovered by culture at the end of the fourth day.

On the first day of the illness 100,000 units penicillin were administered intrathecally and 50,000 units were given every 3 hours intramuscularly, with 2 Gm. sulfadiazene intravenously every 4 hours.

Fifty c.c. of 50 per cent intravenous glucose and later 1,000 c.c. of 5 per cent glucose in normal saline were given with the sodium sulfadiazene. On the following day 3,000 c.c. of 5 per cent glucose in Ringer's lactate solution were administered.

Sedatives as sodium Amytal were employed occasionally to induce sleep.

2. *Meningismus*.—Shortly after the appearance of the latter case of meningitis there were fifteen parturients who developed symptoms of meningeal irritation following therapy with caudal anesthesia. Duration of anesthesia ranged from 55 minutes to 135 minutes, 45 c.c. to 85 c.c. of 1.5 per cent Metycaine solution being administered. These cases appeared within a twenty-four-hour period and presented varying degrees of meningismus. Few of them complained of headache; more than half of them had nuchal rigidity and hyperactive deep reflexes, and in all of them a positive Kernig sign was elicited. Temperature remained normal throughout the postpartum course; symptoms and signs began to disappear after the second postpartum day. All recovered promptly without sequelae and were discharged on the seventh postpartum day.

The spinal fluid of one of this group was removed without pressure. The fluid was clear with 200 cells, 95 per cent polymorphonuclear leucocytes. Smear and culture were negative.

Discussion

The anesthetic drug employed was 1.5 per cent Metycaine solution. This was made up from ampules by the hospital anesthetist. However, after the fifteen cases appeared with the syndrome of meningeal irritation, the Metycaine solution has been supplied by Eli Lilly & Co. in containers ready for use in each case. More than 1,000 cases have been handled since this change without recurrence of these complications.

There was no evidence to indicate an inadvertent penetration of the anesthetic solution into the subarachnoid space in all of the foregoing cases.

Summary

1. The meningeal complications following successful therapy with continuous caudal anesthesia are summarized.

2. Two cases of meningitis, one of which is reported herein, were encountered. Recovery without sequelae followed in both instances.

3. The syndrome of meningismus of varying degree, typical of a group of fifteen cases, was presented in brief.

Acknowledgment is hereby given to Dr. Abraham Koplowitz for his advice and cooperation and to Dr. Harry Warwick for his kindness in contributing his case of meningitis.

MENINGITIS AND MENINGISMUS AS COMPLICATIONS FOLLOWING CONTINUOUS CAUDAL ANESTHESIA

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SINCE Hingson and Edwards¹⁻⁴ first published their experience with employment of continuous caudal anesthesia during labor and delivery, the number of cases similarly treated has steadily increased. More than 200,000 cases have been compiled.⁵ The complications noted have been indeed few and meningitis following successful therapy would seem to occur but rarely. The occurrence of meningitis as a complication following caudal anesthesia has appeared in reports of three cases^{6, 7, 8} which have been published to date.

Our experience at Beth-El Hospital deals with approximately 7,500 parturient cases. Reports of 250 cases⁹ and 2,300¹⁰ cases, respectively, have been published. Following successful therapy with caudal anesthesia of more than 6,000 parturients, several cases of meningeal complications were encountered. A résumé of these and a case report of one of the meningitis patients follows.

1. *Meningitis*.—There were two cases of meningitis as complications following the administration of caudal anesthesia. These cases were dissimilar only as to the severity of the clinical course and duration of illness. Both cases presented spinal fluid findings as increased spinal fluid pressure and cytology predominantly polymorphonuclear leucocytes. However, no bacterial agent was discovered; the smears and cultures were negative. Recovery was complete in both instances.

The first case had a relatively mild course and was discharged in good condition on the seventh postpartum day.

The second case is detailed: A. S. is a 27-year-old, white, para i, gravida ii, who was admitted to the hospital Aug. 21, 1947, in active labor. Temperature 98.6° F., pulse 80, respiration 20, blood pressure 112/70, urinalysis negative.

Continuous caudal anesthesia was administered for one hour and thirty minutes; 60 c.c. of 1.5 per cent Metycaine solution was used. Labor was uneventful. She was delivered of a 7 pound, 1 ounce living male child with low forceps and episiotomy. The total duration of labor was thirteen hours.

Headache and projectile vomiting developed three hours later; shortly following this there was nuchal rigidity and hyperactive deep reflexes; Kernig and Brudzinski signs were positive, bilaterally. She had twitching of the orbicularis oculi and levator palpebrae muscles. Six hours following delivery she was disoriented, became incontinent and comatose. Clonic convulsive seizures recurred during the several hours which followed. Generalized muscular flaccidity appeared and the deep reflexes disappeared. Coma persisted throughout the second postpartum day and her condition improved by the end of that day. Consciousness returned and she began to utter sounds; speech was in monosyllables. Improvement continued gradually and by the end of the sixth postpartum day she became alert, responded to questions, and possessed memory of recent events. Subsequently she improved more rapidly; her memory of remote events returned. The patient became cooperative and by the thirteenth day she recovered completely, being neurologically negative with a normal spinal fluid. On the fourteenth postpartum day she was discharged.

THE USE OF AN ESTROGENIC CREAM IN THE TREATMENT OF SENILE VAGINITIS

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VULVOVAGINITIS, atrophic vaginitis or senile vaginitis—atrophic conditions of the vaginal mucous membrane usually associated with hypo-estrinism—has long been a therapeutic puzzle. Atrophy may be present in normal postmenopausal women without causing symptoms. However, when a condition or conditions such as itching, burning, dyspareunia, vaginal discharge, and an acute inflammation develop, the discomfort of the patient is often very marked. It has been known that estrogenic hormones given by injection or by mouth may relieve these symptoms, but often the dosage must be pushed so high that irregular or withdrawal bleeding may result. The use of an estrogen in a cream base, applied topically in the vagina by means of an applicator containing .446 mg. of dienestrol when full, has been reported by A. E. Rakoff, M.D. ("A Clinical Evaluation of Dienestrol, a Synthetic Estrogen," *J. Clin. Endocrinol.*, October, 1947) to help cure this condition without producing detectable side effects.

In the course of this study the new potent estrogen, dienestrol, in a cream base,* was given to every patient in the Gynecological Out-Patient Clinic of the New York Hospital who complained of symptoms associated with senile vaginitis, unless there was indication of specific infection or disease. Although a large number of patients received this medication, only 123 have had sufficient follow-up at the present time to be reported here.

At the time of her first visit, each patient was given one tube of cream, instructed to use, every night, one applicatorful (4.46 Gm. of cream containing 0.446 mg. of dienestrol) and to return to the Clinic in one, two, or four weeks, depending upon the severity of the condition. If there was a four-week interval between visits, the cream was used up several days before her return visit. Some patients were subjectively and objectively cured in one or two weeks, and no more cream was given, but usually a second tube was necessary even though the improvement was apparent. All patients were examined at each visit. Vinegar douches were prescribed only when one of the complaints was that of a discharge. If the patient had a recurrence after discontinuing the cream, she was told to resume its use only as frequently as necessary to prevent discomfort, which usually meant once or twice a week. No complications were noted, even in those patients who used the cream irregularly for as long as twelve months. One patient, whose symptoms had improved, developed a definite rash two weeks after beginning treatment, but this disappeared when the cream was discontinued. There were no other reactions noted. One patient, aged 60, who was improving, showed some irregular uterine bleeding after using the cream daily for several months, but this subsided when the amount of cream was reduced to one-third applicatorful daily.

In the 123 cases, 84, or 68.3 per cent, were definitely improved both subjectively and objectively, or were cured; 31 cases, or 25.2 per cent, were classed

*The estrogenic cream (Dienestrol Cream) used in this study was supplied by the Ortho Pharmaceutical Corporation, Raritan, N. J.

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the interpretation that a concentration of the toxic products of placental necrosis (histamine ?) on the adjoining maternal arteries, causes vascular damage, rupture, and hemorrhage.

In fulminating abruptio placentae, the infarction is of the early "E" type and often very extensive, involving one-half to two-thirds of the placenta (Figs. 1, 2). In this case, widespread damage to the underlying maternal arteries takes place, causing extensive extravasation, hemorrhage, and complete separation of the placenta.

In summary, therefore, abruptio placentae should be considered as one of the three possible terminations of true toxemia of pregnancy after reaching the severe or pre-eclamptic stage, namely (1) abruptio placentae, (2) eclampsia, and (3) eclampsism.

Discussion

Despite the pioneer work of Young⁴ of Edinburgh in 1914, confirmed by our own investigations of the past fifteen years, also by Hunt, Patterson, and Nicodemus,⁵ and in more recent years by Falkiner of the Rotunda,⁶ the significance of acute and subacute hemorrhagic placental infarction continues to be questioned or denied. Failure to confirm these findings may possibly be attributed to attempting to cut and interpret the placental strips in the fresh state, rather than in the fixed state by use of ten per cent formalin for several weeks.

Classification, Etiology, and Effects of Placental Infarcts

There are two types of infarcts in the placenta, namely (1) the anemic and (2) the hemorrhagic. The anemic type, "A" and "B" (7, Figs. 1, 3) is undoubtedly due to obliterative endarteritis (8, Fig. 1) which very gradually shuts off fetal circulation to the dependent placental tissue. Slow necrosis of the villi occurs, inducing thrombosis of the intervillous maternal blood, which becomes hyalinized. The villi and their blood vessels are normal in size and are often termed "ghost villi" since they are pale, anemic, and do not stain (8, Figs. 2, 3).

Grossly, the anemic infarct is white, occasionally slightly yellow, and is very firm. It is usually found near the margin of the placenta where the arteries are small and more apt to be obliterated. Slow necrosis minimizes toxic products and the surrounding hyalinized maternal blood precludes dissemination into the maternal circulation. Anemic infarction, therefore, should have no relation to toxemia and this is found to be the case, on comparing the clinical and placental findings.

The acute hemorrhagic infarct, as seen in the formalin-fixed placenta, appears as a dark oval or round area, sharply demarcated from the surrounding normal light-colored placental tissue. The extent of the acute infarction varies all the way from an isolated round or oval area, one to several centimeters in diameter, to an elongated area of infarction, extending through one-third, one-half, or even two-thirds of the width of the placenta. (Figs. 2, 3.) *The isolated and confluent forms* of the infarction take on much significance, as will be seen in discussing the probable cause of the infarction.

The consistency is still soft and spongy as the villi have not yet broken down. For this reason, the lesion does not shine or reflect the light when the strip is held toward the light, horizontally to the line of vision. On bending the entire strip, the infarcted area bends with it.

Microscopically, if one has cut the block to include both the light and dark tissue, the light tissue is seen to be normal, the villi being of normal size,

as unimproved because they showed either no clinical improvement or were symptomatically no better. However, many of these patients were better either clinically or symptomatically than when they were first seen. In 2 cases, or 1.6 per cent, the condition was aggravated. and 6 cases, or 4.9 per cent, could not be evaluated because of other complications such as trichomonas or monilia infections which developed after dienestrol therapy was begun, or because the patients were given oral estrogenic therapy for menopausal symptoms soon after this treatment was started.

We were particularly interested in 80 of the total number of cases who returned to the Clinic in from one to four weeks after receiving the estrogenic cream. The complaints of these 80 were as follows: itching, 36; discharge, 29; burning, 17; spotting, 7; dyspareunia, 8; with some patients presenting more than one complaint. The diagnoses made were: senile vaginitis in 63 cases; pruritis vulvae, 3; leucoplakia, 5; kraurosis, 1; and others such as vulvovaginitis, vulvitis, and traumatic vaginitis in 17; some cases having more than one diagnosis. We have divided these 80 as follows:

FOLLOW-UP IN	CONDITION		
	IMPROVEMENT	NO IMPROVEMENT	AGGRAVATED
1 week	8	4	1
2 weeks	26	7	0
3 or 4 weeks	25	9	0
Total	59	20	1

The 43 remaining patients, of whom six were eliminated as explained previously, did not return until after at least four months and of these, twenty-five were improved, eleven unimproved, one worse.

The cream was used also on two children having a nonspecific vaginitis, one aged 6 and the other 10 years. In both cases the discharge cleared up very promptly and did not recur. However, because of the possible unpleasant complications associated with vaginal manipulation in children, we believe that some other form of therapy is preferable.

Although previously it had been thought that an estrogenic cream was contraindicated in leucoplakia, dienestrol in a cream base was prescribed for five such cases only as a means of controlling the extreme itching and excoriation, with quick and excellent results in four cases.

Summary

In this investigation 123 patients received dienestrol in a cream base for the treatment of atrophic changes occurring in the vaginal mucosa. All of these patients, with the exception of two children and two adults, were over 40 years of age. In 68.3 per cent of the cases, after receiving this type of therapy, the vaginal mucosa appeared healthy and the patients had no complaints. Those patients who returned to the Clinic at the end of one week of treatment showed rapid improvement. Although 25.2 per cent of the cases were classified as unimproved, it must be noted that some of this group showed either symptomatic or clinical improvement. Relief of symptoms had to be accompanied by clinical response before the patient was considered improved. Further topical application of the estrogenic cream was prescribed if symptoms recurred. The average healthy vagina was maintained in some instances by using dienestrol one to three times a week over a period of months. No untoward effects were noted.

SPONTANEOUS RUPTURE OF A NORMAL UTERUS ASSOCIATED WITH PLACENTA ACCRETA FORMING A CENTRAL PLACENTA PREVIA

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THE spontaneous rupture of a normal uterus before the onset of labor is an exceedingly rare obstetrical emergency. Generally speaking, the incidence of rupture of the uterus varies from one in 95 (Whitacre and Lang, Peiping Union Medical College*) to one in 3,029 (Dugger, County of Philadelphia, Pennsylvania, 1945). A figure of one in 2,000 approaches the average reported.

Mrs. M. D. A., a white woman, aged 30 years, was admitted to the Charity Hospital at New Orleans on Jan. 6, 1947, at 3:30 P.M. Her last menstrual period was March 5, 1946, and expected date of confinement, Dec. 12, 1946. Her only other pregnancy eight years before terminated in a difficult breech delivery after a forty-eight hour labor, followed by postpartum hemorrhage, manual removal of the placenta, and morbidity which persisted for one week. No surgical procedures and no abortions, spontaneous or induced, were admitted.

The present pregnancy, under the supervision of her family physician, had been uneventful except for a few days' hospitalization at the sixth month for vaginal bleeding which subsided with bed rest and progesterone.

On the evening before admission the patient noted mild lower abdominal cramps which were not sufficient to keep her awake. She was awakened, however, at 3 A.M. with a moderately severe constant abdominal pain. She entered the local hospital at 7 A.M., at which time her physician saw her. After three to four hours during which several examinations revealed no progress in labor, the pain became much more intense and flat plate of the abdomen revealed the fetus in a transverse position. She was then sent to New Orleans by ambulance. No sedatives and no oxytocics were given. A slight amount of vaginal bleeding occurred en route.

Physical examination on admission revealed an acutely ill, markedly obese woman in profound shock. The blood pressure was unobtainable and the pulse 150. The abdomen was somewhat distended, and the lightest palpation caused the patient to react violently. The remainder of the examination was negative except for a pallor of the palms, nail beds, and mucous membranes.

The blood pressure rose to 120/90 shortly after a transfusion of whole blood was begun. Vaginal examination disclosed a long hard cervix admitting one finger to the internal os. No presenting part could be felt through the lower segment. No vaginal bleeding occurred. An x-ray plate of the abdomen revealed the fetus in a transverse lie, with the head on the mother's right.

Catheterized urine on admission showed 2 plus albumin, sugar negative. Sediment contained granular casts and 10 to 20 white blood cells per high power field. The admission hemoglobin was 10.5 Gm. The Kline and Kolmer tests were negative.

A tentative diagnosis of rupture of the uterus versus premature separation of the placenta with concealed hemorrhage was made and the patient was laparotomized under ethylene and ether anesthesia. A second and a third transfusion were given during the operation. A

*The incidence of pelvic deformities associated with osteomalacia and the prevalence of untrained midwives is held accountable for these figures.



Fig. 1.—Specimen as seen from above.

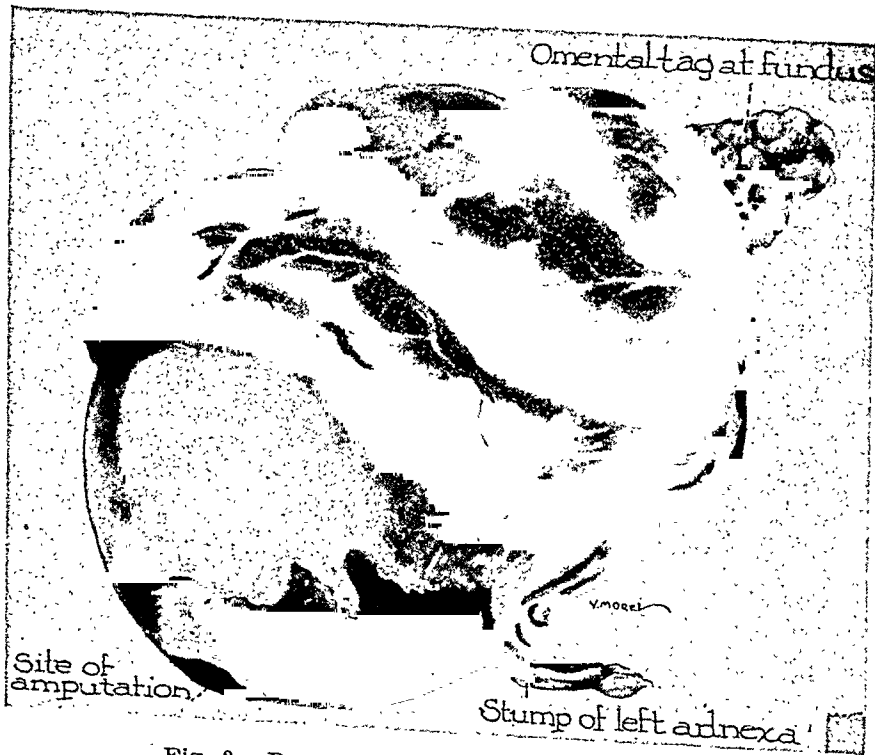


Fig. 2.—Drawing of lateral view of specimen.

midline subumbilical incision was made and when the peritoneum was opened the cavity was seen to be filled with blood and the dead fetus was lying free in the upper abdomen. The rent in the uterus was transverse across the fundus from one cornu to the other. The placenta was still attached and occupied the position of a true placenta previa centralis. The uterus was firmly contracted. An omental adhesion was noted on the posterior aspect of the fundus. After removal of the fetus, a subtotal hysterectomy was done with the placenta in situ.

Subsequent microscopic section through the site of placental attachment revealed chorionic villi deeply invading the uterine myometrium—a placenta increta (Irving and Hertig).

Convalescence was marked by temperature elevation to as high as 101° F. to the fifth postoperative day and a moderate ileus for forty-eight hours. Penicillin, 50,000 units every 3 hours, had been started just prior to operation. The patient was discharged on the eighth postoperative day, and has been seen twice in the postpartum clinic and is in excellent health.

Summary

An unusual case report is presented in which spontaneous rupture of an apparently normal uterus occurred in conjunction with a placenta accreta which formed a central placenta previa. The mother recovered. The only clues as to previous uterine trauma were the history of a long hard breech delivery, and the finding of an omental adhesion near the site of the rupture. No oxytocic drugs had been administered.

MYASTHENIA GRAVIS COMPLICATED BY PREGNANCY*

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THIS is only the second case of myasthenia gravis complicated by pregnancy which we have had in the history of the Evanston Hospital.

The patient, Mrs. J. M. C., aged 27 years, para i, was sent to me by Dr. L. Blakeman of Chicago. This patient was also seen in consultation a few years ago by Professor Veit of Harvard. The weakness complained of most is that in the right arm and leg. The patient is 5 feet 6 inches tall, and when first seen, 7 months pregnant, she weighed 169 pounds. Her average weight, however, is 155. Her only medical history was that of an appendectomy at the age of 17 and a pilonidal cyst removed at the age of 16 years. Diagnosis of myasthenia gravis was first made in 1944. There was no anemia in this case, the lowest blood count being hemoglobin of 81 per cent and red blood cells 3,840,000. This patient, as stated before, when first seen weighed 169, but just before delivery she had lost 3 pounds and the weight at that time was 166. There was no evidence of any toxemia. The patient was Rh negative and married to a husband who was Rh positive. When first seen, this patient was taking a routine dose of Prostigmine but was unable to walk at any one time more than two blocks. She could start out from her home and by stopping frequently she could walk to the end of the block in which she lived, rest a while, and return to her apartment. She was also unable to do housework for any length of time. She could, by resting frequently, not become too fatigued after she had attempted some simple housework.

She went into labor on Sept. 4, 1947, at about 9 A.M. and by 11 A.M. was having strong, four-minute pains. By 2 P.M. the pains were every two minutes and quite normal in strength and character. At 7 P.M., however, she had only 2 cm. dilatation. At that time her pulse was 105, her eyelids were drooping, she found it very difficult to swallow and speak and her respirations had increased. Due to the fear of a respiratory collapse, it was deemed advisable to terminate the labor. This was then done under local anesthesia at 8:30 P.M. after approximately eleven hours of labor.

During her labor she received Seconal, grains $1\frac{1}{2}$, at 11:15 A.M. At 4:50 P.M., we started 1,000 c.c. of 5 per cent glucose in water. At 4:50 P.M. she received another ampule of Prostigmine and at 4:30 P.M. she was given 50 mg. of Demerol. At 7:15 P.M., prior to operation, she was given scopolamine, $\frac{1}{150}$ grain. The bag of waters was intact and the delivery was effected under a local 1 per cent procaine anesthetic. After delivery, she was given Prostigmine 1-2000, 1 c.c. twice a day and aspirin and codeine for pain. She found it possible to enter into about the same amount of activity following operation as the average patient, except that her periods out of bed were somewhat shortened as she would become short of breath and unduly fatigued. She left the hospital on the twelfth postpartum day and at home is still using Prostigmine. She was last seen on March 8, 1948, and at that time could care for her baby to some extent, but was somewhat confined to the house except for special occasions.

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HEMORRHAGE FROM A RUPTURED VARICOSITY IN THE PLACENTA WITH DELIVERY OF A LIVING FETUS

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THERE is only one mention of this condition in a textbook¹ and only two similar cases have been reported.^{2, 3} The fetus was lost in both of the latter.

Mrs. M. C. D., aged 19 years, married six months. She became pregnant in April, 1947. Her expected date was calculated to be around Jan. 11, 1948. She had a normal antepartum period.

On Dec. 25, 1947, she was admitted to the hospital in labor at 11:30 A.M. Her pains were regular at intervals of five minutes lasting thirty to forty-five seconds. Her condition was good. The fetal heart tones, 120, were heard in the right lower quadrant. Blood pressure was 120/80; urinalysis was negative. She progressed normally and at 3 A.M. on Dec. 26, 1947, she was taken to the delivery room, with the cervix completely dilated. The membranes were intact and bulging through the labia, the head was on the perineum, the rectum was bulging. At 3:25 A.M. the membranes ruptured spontaneously and there was a gush of bright red blood from the vagina.

A low forceps delivery was immediately performed and a living male infant weighing five pounds, three ounces was delivered at 3:30 A.M., followed by a large gush of grossly bloody amniotic fluid when the body of the baby was delivered. The placenta was expressed in about three or four minutes. There were just a few small clots and a little fresh bleeding. The placenta was of moderate size, well developed, and showed no evidence of retroplacental hemorrhage nor infarcts. There was no evidence of placenta previa marginalis. The cord was attached a little off the center, was of moderate length, and showed no abnormalities.

Examination of the fetal surface of the placenta showed several patches of ecchymosis under the amnion. Closer inspection revealed a small opening on the fetal surface of the placenta, which evidently was the site from which the hemorrhage had occurred. The lesion was a rupture of a small varicosity about 4 mm. in diameter, located about 4 cm. from the periphery on the fetal surface of the placenta.

The hemorrhage was entirely fetal, none of it was coming from the mother. In Leff's case³ the membranes ruptured six hours previous to the delivery and the child was stillborn. Rannenbergs case² resulted in a delivery of a stillborn fetus.

As Leff states, "What to do at the time of the hemorrhage is the problem to decide." Placenta previa and extensive separation of the placenta must be ruled out. If the fetus is dead and the mother is in good condition interference is not warranted. If the hemorrhage occurs when the cervix is not dilated, the fetus would probably be dead before a cesarean section could be done. In this case it was fortunate that the cervix was fully dilated, the baby small, and the forceps were ready for routinely lifting the head over the perineum in a primipara.

Rupture of a velamentous cord resembles this condition and two such cases have been reported by Kosmak.^{4, 5}

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Department of Reviews and Abstracts

Selected Abstracts

Abortion

Whitacre, Frank E., Hingson, Robert A., and Turner, Henry B.: *The Treatment of Eclampsia by Means of Regional Nerve Block*, South. M. J., page 920, Oct., 1948.

The clinical and pathological evidence supports the concept that eclampsia is the result of angiospasm. The electro-encephalographic tracings taken during convulsive seizures are typical of those induced by anoxia which in the case of the eclamptic results in angiospasm. The pressor substances probably originate in the placenta.

Regional nerve block controls the hypertension and convulsions of eclampsia through sedation and vasodilatation. This is followed by increased renal circulation which favors an increase in urinary output, reduces blood pressure, and thus relieves the cardiac load. This in turn prevents pulmonary edema, the most common avenue of exit for the eclamptic. The absence of severe narcosis in babies is an important factor in evaluating the regional nerve block in the treatment of eclampsia. Regional anesthesia is induced by continuous caudal administration of a 1.5 per cent solution of Metycaine in a dose of one to two c.c. each hour. Anesthesia is maintained throughout labor and the results have been gratifying.

WILLIAM BICKERS.

Kriseman, M. M.: *Intrauterine Penicillin*, Edinburgh M. J., page 293, May, 1948.

The author reports seven cases of incomplete abortion, one case of septic abortion, and two cases of local uterine puerperal infection, and one case of functional uterine bleeding treated with intrauterine penicillin. Two techniques are given, one continuous and the other intermittent. In both techniques a rubber catheter is sutured through the cervix. In the continuous method, 500,000 units of penicillin are diluted in 500 c.c. of normal saline and instilled in the uterus at the rate of 30 to 35 drops a minute. Approximately 2,000,000 units are given every 24 hours. In the intermittent method, the penicillin is instilled at three-hour intervals. The author has shown that penicillin is absorbed from the uterine cavity and produces effective bacteriostatic levels in the blood stream. It is suggested that this method might be used prophylactically and also might be of advantage in combating anaerobic streptococcus infection and infections with the *Clostridium welchii*.

L. M. HELLMAN.

Cancer, Malignancies

Marks, Joseph H., and Wittenborg, Martin H.: *Results of Treatment of Carcinoma of the Ovary With Data on Age, Incidence of This Disease*, Surg., Gynec. and Obst., page 541, Nov., 1948.

The authors report a series of 76 patients with carcinoma of the ovary, 57 of whom were followed until death. Fourteen showed a five-year survival rate. Although not all the patients had an opportunity to live five years, the calculated five-year survival rate was 21 per cent. The authors believe that surgery for carcinoma of the ovary should

be accompanied by x-ray therapy in all cases. They state that it is excellent insurance postoperatively. It may occasionally result in a cure even in advanced stages of the disease. The authors believe that the surgeon should not risk the patient's life with too meticulous removal of the carcinoma but that he should remove the easily accessible masses and then rely on x-ray. They state that x-ray therapy may bring gratifying relief even when cure is not achieved. The age, specific incidence in 494 cases of carcinoma of the ovary is shown. There was a definite decrease in the incidence of this type of carcinoma after the sixth decade. It, therefore, differed radically from other types of malignant tumor, which show an increase in incidence with age. L. M. HELLMAN.

Sicard, Andre: The Frequency of Ovarian Metastases From Carcinoma of the Breast, *Presse Med.* 56: 606, Sept. 4, 1948.

The author, after reviewing 38 cases of breast carcinoma as related to surgical castration to control hormonal influence of the ovaries upon breast neoplastic metastases, found these observations after dividing his series into two groups: (1) In a subgroup of 23 women submitting to mastectomy, he discovered in two women microscopic ovarian metastases upon removal of the ovaries, an incidence of 11.0 per cent. In all instances the patients presented no clinical evidence of metastases. (2) In a second group of 15 women having obvious bone, nerve, or organ metastases, early or late, following mastectomy, he found ovarian metastases in nine cases, an incidence of 60.0 per cent.

Sicard concludes that surgical castration is, therefore, indicated after mastectomy for carcinoma of the breast if one would control metastasis. He found radiotherapy inadequate. CLAIR E. FOLSOME.

Emge, Ludwig A.: Six Cases of Primary Carcinoma of the Fallopian Tube, *West. J. Surg.* 56: 334, June, 1948.

Six cases of primary carcinoma of the tube are reported among tubes removed from 2,000 patients, an incidence of 0.3 per cent. The vagaries of symptomatic manifestations obscure preoperative diagnosis to such a degree that early recognition of tumor is impossible. The author admits that he has nothing new to offer which might aid in early diagnosis, but he does emphasize the need for surgical exploration of obscure pelvic lesions when seen during the fifth and sixth decades of life. The more universal employment of the Papanicolaou smear and the more frequent use of hysterosalpingography may offer something for the future. WILLIAM BICKERS.

Acosta-Sison, H.: Dangers of Myometrial Chorionepithelioma Caused by Failure of Early Diagnosis, *Philippine J. Surg.* 2: 240, Nov.-Dec., 1947.

Chorionepithelioma originating in the myometrium, without an endometrial focus, is most difficult to recognize clinically. Uterine bleeding is apt to be mild and delayed and curettement does not retrieve tumor tissue. Recognition thus disguised, the growth extends toward the uterine serosa. Intraperitoneal hemorrhage may force a diagnostic laparotomy.

Of 46 cases of chorionepithelioma admitted to the Philippine General Hospital in three years, eight were primary in the myometrium. In five of these, abnormal bleeding did not appear until 14 to 36 months after expulsion of the conceptus. In the one case so tested, the Friedman reaction was negative.

In addition to pregnancy gonadotropin titration, the author recommends his "HBEs method" for diagnosis. This is (H) a history of expulsion of an abortus, a term pregnancy, or a mole, (B) uterine bleeding, and (1) enlargement and softening of the corpus uteri. Unless there is a current abortion, this syndrome may signify a myometrial chorionepithelioma. IRVING L. FRANK.

Savran, J., Sayer, E. A., and Schradiak, C. E.: Primary Malignant Melanoma of Female Urethra, *Am. J. Surg.*, page 743, May, 1948.

The authors briefly review the literature of the fourteen reported cases with this lesion and add one of their own. This reported melanoma was treated by local excision and her course was one of steady decline until her expiration 19 months later. No autopsy was performed.

S. B. GUSBERG.

Cesarean Section

Ritala, A. M.: A New Modification of the Technique of Cesarean Section, *Acta obst. et gynec. Scandinav.* 26: 604-609, 1946.

The author presents, with aid of eight drawings and four photographs, a modification of cesarean section. He utilizes the round ligaments to peritonealize and strengthen his repair of the uterine incision. Ritala contends this method offers two advantages: (1) prevention of scar in subsequent pregnancy, and (2) correction of uterus to normal ante-flexed position.

CLAIR E. FOLSOME.

Perez, Manuel Luis, and Echevarria, Ramon: Intraperitoneal Sulfonamide Prophylactic Treatment and Penicillin Therapy in Potentially Infected Cesarean Sections, *Rev. obst. y ginec.* 7: 166-197, 1947.

The authors collect several series of cesarean sections treated with intraperitoneal sulfonamides and penicillin therapy. Twenty-six cases were from the T. De Alvear Maternity Hospital; eight cases from the senior author's private practice; nine cases from the junior author's private practice and twenty-six cases from the private practices of Drs. de la Colina, Rosenvasser, and Monti.

In all sixty cases the patients received 4 to 6 Gm. of sulfonamide powder intraperitoneally at time of the section. In several instances the sulfonamide dusting included application of it into the uterine cavity and wound. With but few exceptions, the patients received, in addition, doses of 20,000 Oxford Units of penicillin every 3 to 4 hours for an average total range of 400,000 to 600,000 units. In a few instances as much as 1,000,000 O. U. were used. Only eight of the sixty cases showed any untoward febrile response. One death occurred in the clinic series. Three patients had delayed hospitalization because of pelvic thrombophlebitis. The majority of the cases left the hospital in 10 to 12 days, some as early as the seventh day and one on the twentieth day. In the fatal case, the patient died of a postoperative accident (fecal fistula and peritonitis) 37 days after her section.

In all 60 instances, the patients gave histories of intrapartum obstetrical complications which would classify them as potentially infected cases. The authors conclude that the simple use of local intraperitoneal sulfonamides with subsequent penicillin therapy is adequate and less hazardous than specialized cesarean section operations.

CLAIR E. FOLSOME.

deCarle, Donald W., and Durfee, Raphael B.: The Pfannenstiel Incision for Cesarean Section, *West. J. Surg.* 56: 360, June, 1948.

Sixty-one cesarean sections have been reviewed from the standpoint of the advantages and the disadvantages of the Pfannenstiel incision. Observations here reported would indicate that the transverse incision is associated with less discomfort and is therefore conducive to early ambulation. When using spinal or caudal anesthesia, a much lower level of anesthesia can be used, sparing the patient the hazard associated with large doses of anesthetic agent. The incision gives adequate exposure for delivery. The cosmetic advantage of this incision especially in the salubrious climate of California whence this article appears may be worthy of mention.

WILLIAM BICKERS.

Endocrinology

Ziskin, Daniel E., and Moulton, Ruth: A Comparison of Oral and Vaginal Epithelial Smears, *J. Clin. Endocrinol.* 8: 146, Feb., 1948.

In this study, the authors show that the changes that take place in the vaginal epithelial smears as a result of hormonal influence are, in part, reflected in oral epithelial smears. The obvious advantage of oral smears over vaginal smears, insofar as the ease of securing them and the emotional reaction of the patient are concerned, is pointed out.

Preliminary studies were carried out on rhesus monkeys. Oral and vaginal smears on a series of 23 women were compared. This group was composed of one girl with secondary amenorrhea, five women who had normal menstrual cycles, ten who were menopausal and had oral complaints such as burning or dryness of the mouth, and seven without oral complaints. From their studies the authors conclude that in the vaginal smear slight hormonal changes are more readily discernible than in the oral smear. The estrogenic response is more clearly demonstrated in the vaginal smear. The ovulation time can be more accurately predicted by the vaginal smear. Finally, in spite of the relative ease with which specimens can be obtained, the oral smear cannot replace the vaginal smear as a method of determining hormone levels in women.

HERBERT J. SIMON.

Stewart, H. L., Jr., Sano, Machteld E., and Montgomery, Thaddeus L.: Hormone Secretion by Human Placenta Grown in Tissue Culture, *J. Clin. Endocrinol.* 8: 175, Feb., 1948.

In this communication the authors offer experimental evidence in answer to the question as to whether or not the placenta is an organ of internal secretion. They grew human placenta in tissue culture and, from the tissue culture washings, biologic hormone titrations were carried out.

From the evidence presented in this paper, it would appear that the Langhans' cells of the placenta produce gonadotropin. It may be further predicated that the syncytial cells produce the estrogen. These hypotheses are substantiated by the fact that human placental tissue cultures result in rapid growth of the Langhans' cells and a corresponding increase in the hormone titrations for the gonadotropins; however, at the same time, the syncytial cells quickly disappear and repeated estrogen determinations fail to reveal its presence. Attempts were made to grow more mature placenta in culture, but were unsuccessful as fibroblasts soon overgrew the culture and there was no syncytial or Langhans' cell growth.

HERBERT J. SIMON.

Eidelsberg, Joseph: Estrogens in Urine and Cytology of Vaginal Smears After the Use of an Estrogenic Cream, *Am. J. M. Sc.* 214: 630, 1947.

In this study an effort was made to establish any demonstrable effect on the estrogen content of the urine and on the cytology of the vaginal smears after the use of an estrogenic cream which contained 7,500 International Units per ounce. The patients were instructed to apply approximately 1/14 of an ounce of the cream to the skin of the face each evening. Thus, about 535 International Units were used daily by the patients. Following proper control studies, the authors were unable to demonstrate any significant fluctuation in the urinary estrogen excretion, or any changes in the cytologic cycles of the vaginal smears. From this they conclude that the use of cream containing 535 International Units of estrogenic substance produces no systemic effect.

HERBERT J. SIMON.

Menstruation, Dysmenorrhea

Usandizaga, Manuel: A General Concept and Nomenclature on Menstrual Disorders, *Tokoginec. práct.* 7: 263-303, June, 1948.

The subject of a more acceptable classification of menstrual disorders had arisen at the First Spanish-Portuguese Congress of Obstetrics and Gynecology. Professor Usandizaga of Santander, Spain, offers a most scholarly paper with detailed explanations underlying the

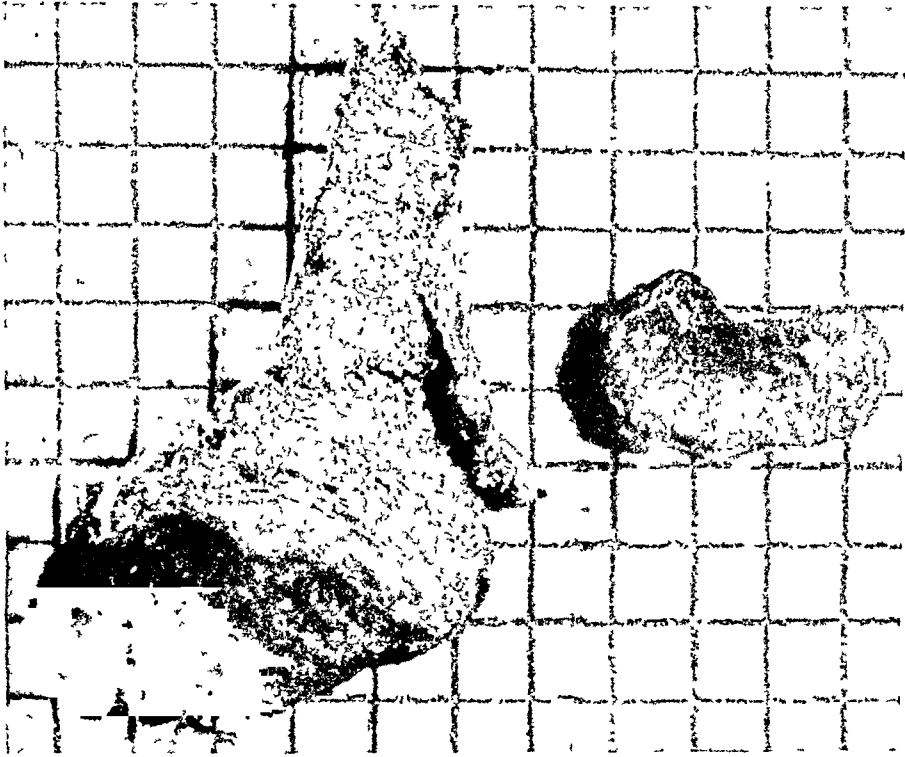


Fig. 6.—Eclampsia and abruptio placentae, Case 42; recent clot adjacent and adherent to underlying older late "E" or "D" hemorrhagic infarction; marginal location of infarction a factor in survival of baby; early "E" hemorrhagic infarction in smaller piece of same placenta probably responsible for simultaneous occurrence of eclampsia.

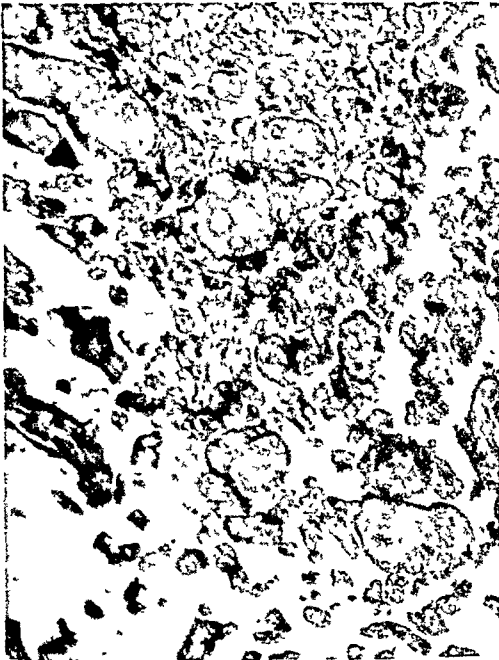


Fig. 7.



Fig. 8.

Fig. 7.—Eclampsia and abruptio placentae, Case 42; low-power magnification at junction of acute hemorrhagic early "E" infarction above and normal tissue below. Same appearance as in Fig. 4.

Fig. 8.—Eclampsia and abruptio placentae, Case 42; higher magnification of subacute hemorrhagic infarction (late "E" or early "D") showing enlarged crowded villi, more advanced necrosis, and distended villous vessels.

Cadarso, J. R., De Guevara, L., and Strecht-Ribeiro, C.: Considerations Upon the Presacral Nerve in Dysmenorrhea, *Rev. españ. obst. y ginec.* 5: 1-12, Feb., 1948.

The authors obtained the specimens of resected presacral nerves from fourteen patients treated by this method for relief of dysmenorrhea, operated upon at Oporto Medical School. The specimens were fixed in 10 per cent formaldehyde or Bouin's solutions and stained with numerous stains including van Gieson, trichrome method of Masson, hematoxylin and eosin and special silver stains.

Among the pathological findings were congestion, perineural edema, perineural sclerosis, and intrafascicular sclerosis. They describe and illustrate pseudoneuronophagia, with nuclear degenerative changes: pyknosis, karyolysis, and alterations in the medullary fibers along with changes in the glial tissue (schwannosis, hyperplastic capsules) are the principal evidence of a predominant inflammatory change. More correctly, the pathological diagnosis of these resected nerves might be discrete neuroganglionitis. Six microphotographs are included.

CLAIR E. FOLSOME.

Miscellaneous

Oeconomos, Nicolas: Vaginal Wounds During Coitus, *Gynec. et obst.* 46: 557-563, 1948.

The author reports on three cases of women with vaginal wounds induced during intercourse who were seen at the Hotel-Dieu, Paris, on the surgical service of Pierre Brocq. The women were 39, 29, and 55 years old, respectively. The first of these cases suffered severe hemorrhages and it required total hysterectomy to control the two-fringe size laceration to the left of the cul-de-sac. The other two cases also had the vaginal wounds on the left wall and fornix. Each of the latter was controlled by tamponage and local repair. In the case of the 55-year-old patient, there had been little sexual exposure after an earlier subtotal hysterectomy for fibroids.

The author gives considerable detail on the literature concerning this subject which in clinical practice is dramatic and requires rapid treatment.

CLAIR E. FOLSOME.

DeLa Vega, J. C.: A Biological Pregnancy Test With Blood Obtained by Puncture of a Pelvic Hematoma, *Bol. Soc. de obst. y ginec. de Buenos Aires* 26: 98-102, Nov. 21, 1946.

The author reports on seven patients, most of whom gave an earlier history of acute abdominal pain, from whom he obtained blood via puncture of the cul-de-sac. In three cases, the Friedman or Hofman pregnancy tests were negative while in the remainder the tests were positive. He concludes the use of blood obtained from the cul-de-sac in these delayed, non-critical cases offers an important diagnostic aid when used in the biological tests.

CLAIR E. FOLSOME.

Udaondo, C. B., and Castex, M. R.: Bony Changes in Gastrectomized Patients, *Presse méd.* 55: 847-848, Dec. 20, 1947.

In view of the knowledge that gastric secretions contain an indispensable factor essential to the absorption of calcium and phosphorus into the intestine, the authors review 41 patients who had submitted to gastrectomy. Thirty eight of this series had had stomach resection for gastroduodenal ulcers, two cases for carcinoma of the stomach, and one case for sarcoma. The patients' ages varied between 24 and 67 years. Thirty-four were men and seven were women. Radiologic studies indicated that 95.12 per cent of the series showed some decalcification of their lumbosacral spine or pelvic bones. The degree of decalcification varied as follows: small amount, 17.0 per cent; discrete areas in 41.4 per cent; moderate decalcification in 29.25 per cent; and heavy losses in 7.31 per cent. In 60 per cent of the series of 26 patients upon whom inorganic phosphorus and calcium determinations of the

placement of each disorder into its proper category. After defining normal menstruation and excluding many of the more frequently used adjectives, he finally arrives at a simple six-point classification. These points are given in the following outlined summary:

- I. Abnormalities in relation to the onset or termination phases of menstruation:
 1. Abnormalities of the menarche: (a) precocious menarche; (b) late menarche.
 2. Abnormalities of the menopause: (a) precocious menopause; (b) late menopause.
 3. Castration: (a) operative castration; (b) radiological castration.
- II. Absence of the periods:
 1. Amenorrhea; 2. cryptomenorrhea—hidden menses.
- III. Abnormal periods with the chief disturbance in rhythm:
 1. Abnormalities in duration of cycle: (a) polymenorrhea; (b) oligomenorrhea.
 2. Abnormalities in volume of bleeding: (a) menorrhagias; (b) hypomenorrhea.
- IV. Arrhythmic periods.
- V. Hemorrhages in relation to the cycle but not appearing at catamenia:
 1. Slightly before the flow.
 2. Immediately after the period.
 3. In the intermenstrual period.
 4. Throughout the entire cycle.
- VI. Phenomena which accompany the cycle:
 1. Premenstrual tension.
 2. Dysmenorrhea: (a) algomenorrhea (colicky abdominal or sacral pain); (b) menstrual molimina.
 3. Intermenstrual pain.

The author considers the entities of metropathia hemorrhagica, persistent corpus luteum cysts, and genital infantilism so well established they should be classed separately. He recommends further that we abandon such terms as ovarian insufficiency, hyper- and hypoeustrination, functional hemorrhages, and also such adjectives as dysfunctional, pubertal, juvenile, and menopausal before the noun hemorrhage.

The author does use terms infrequently used in the States, but which aptly describe certain symptoms, viz.: (a) *algomenorrhea*, painful menses of colicky type; (2) *spanomenorrhea*, infrequent and scanty flows; (3) *cumenorrhea*, consistently normal periods; (4) *opsomenorrhea*, tardy menstrual periods, and (5) *proiomenorrhea*, premature menstrual flows.

The article is unusually well organized and based upon an excellently documented bibliography of 104 titles.

CLAIR E. FOLSOME.

Ingersoll, Francis M., and Meigs, Joe V.: Presacral Neurectomy for Dysmenorrhea, New England J. Med. 238: 357, March 11, 1948.

This paper deals with a series of presacral neurectomies performed for relief of dysmenorrhea. A total of 111 operations have been done at the Massachusetts General Hospital and the Palmer Memorial Hospital from 1930 to 1946. In most cases the neurectomy was combined with dilatation and curettage, a suspension, and any other necessary pelvic surgery that the gynecologic situation demanded.

By essential dysmenorrhea is meant painful menstruation that severely upsets the social and economic life of the patient; physical examination being negative. There were 89 such cases. In the acquired dysmenorrhea group there were nineteen cases, with sufficient pelvic pathology present to explain their dysmenorrhea.

The authors state that previous reports have adequately demonstrated the efficacy of presacral neurectomy in essential dysmenorrhea, which is now a standard operative procedure in pelvic surgery. They report in this series that complete relief was obtained in 81 per cent of essential and 52.6 per cent of acquired dysmenorrhea. There were twelve failures after presacral neurectomy for essential dysmenorrhea. These failures are accounted for on the basis of either regeneration of sympathetic nerves, incomplete operation, or dysmenorrhea as a manifestation of a psychoneurosis. Twenty-four women had babies postoperatively; labor was painless for 33.3 per cent.

JAMES P. MARR.

The comparative results are given, using this test and simultaneously the conventional Aschheim-Zondek test on the same urine. In addition, the hyperemic response elicited under various known experimental conditions is described. From these experiments, they deduced that it is best to allow four to six hours to elapse between injection and sacrifice of the animals, though there appeared to be no advantage to lengthening the interval to sixteen hours.

The strongest hyperemic response was obtained most uniformly in the heavier test animals (weighing 55 to 70 Gm.). This study demonstrated the desirability of establishing the responsiveness or refractoriness to chorionic gonadotropin. The authors chose albino rats of the Wistar strain.

Attention is called to the fact that, in cases of disturbed pregnancy such as threatened or incomplete abortion or ectopic pregnancy, where an intermediate type of response in the Aschheim-Zondek test is found, the hyperemia test is of little diagnostic value. However, the rapidity and simplicity of the test, together with its high degree of accuracy, in cases of normal pregnancy, make it a valuable diagnostic procedure.

HERBERT J. SIMON.

Newborn

Ware, H. Hudnall, Jr.: Abnormal Presentation, J. A. M. A. 137: 448, May 29, 1948.

The author reviews the various types of abnormal presentation and discusses the treatment of each. Throughout the discussion the author stresses the importance of pelvic measurements prior to the onset of labor, and a careful estimate of the fetal size, especially the fetal head.

WILLIAM BERMAN.

Nielson, Harriet K., Ferris, Deward O., and Logan, George B.: Injury of the Penis, Scrotum and Buttocks of the Newborn Resulting in Gangrene, Am. J. Dis. Child. 75: 85, Jan., 1948.

The case report from the Division of Surgery and the Section of Pediatrics of the Mayo Clinic concerns a multipara who after a twenty-four hour labor delivered herself of a male child with a breech presentation. At the time of delivery the scrotum was estimated the size of a grapefruit and the penis to be red and about four times normal size.

Twenty-four hours later the baby was admitted to the hospital. A support was applied to the scrotum. Penicillin, in doses of 5,000 units, was given intramuscularly every three hours for thirty-nine days. Lines demarcating the gangrenous lesion formed on the penis, scrotum, and buttocks on the fourth day. On the sixteenth day, gangrenous material was removed and the testes exposed and examined.

Primary skin grafting could not be carried out because of infection. Therefore, granulation and epithelization were encouraged in order to bring together the edges of the remaining part of the scrotum.

The patient returned to the clinic one year later, at which time the left testis seemed small and fibrotic. The right testis seemed about normal in size.

Photographs are inclosed showing the preoperative condition and the postoperative results.

JAMES P. MARR.

Franklin, H. Charles, With the Technical Assistance of Loeb, Laura N.: Bacterial Flora in Eyes of Newborn Infants During First Forty Hours of Life—After Single Instillation of Penicillin and Silver Nitrate, J. Pediat. 32: 251, March, 1948.

This report is from the Department of Obstetrics and Gynecology at the University of Tennessee College of Medicine. The study treats of the bacterial flora in the eyes of 200 infants during the first forty hours of life. One hundred were studied after prophylaxis employing a single instillation of penicillin, and 100 after a single instillation of silver nitrate.

serum and plasma alkaline phosphatase activity values were made, a normal calcemia was found but all in lower normal limits. All of these cases showed a normal phosphatemia or a slight elevation.

The authors conclude that the decalcification of the lumbosacral and pelvic bones in gastrectomized patients is extremely important. Clinicians must, therefore, consider supplemental therapy in such cases and recognize that other gastric disturbances may cause serious bony changes. Prevention with proper medication may preclude such bony changes.

CLAIR E. FOLSOME.

Mack, Harold C., Parks, A. E., and McDonald, Marian: Further Observations on the Pregnandiol Test, *Harper Hosp. Bull.* 6: 33, 1948.

A test for pregnandiol in the urine depending upon the precipitation of unpurified pregnandiol has previously been described; the technique is again described in this article. With this simplified test, the findings closely parallel those obtained with the more elaborate quantitative methods. In normal menstrual cycles, in which the excretion of pregnandiol was correlated with the basal body temperature curve, it was found that excretion of pregnandiol followed the postovulatory rise in temperature. In one case in which a planned pregnancy followed ovulation, temperature levels were sustained and pregnandiol excretion continued, as is typical of normal pregnancy. In cases with irregular cycles, with delayed ovulation, pregnandiol excretion also occurs late in the cycle.

The pregnandiol precipitation test has been employed in conjunction with the Friedman test for all specimens submitted for the diagnosis of pregnancy. In 306 urine samples, from patients subsequently found to be pregnant, positive pregnandiol tests indicated a diagnosis of pregnancy correctly in 291 instances (95.1 per cent); there were 15 incorrect negative diagnoses (4.9 per cent). The Friedman test on 280 of these urines gave a correct positive diagnosis of pregnancy in 268 cases (95.7 per cent) and a false negative in 12 cases (4.3 per cent). In 275 urine samples from patients who were subsequently found not to be pregnant, the pregnandiol test was negative in 245 (or 89.1 per cent), and falsely positive in thirty, (or 11.9 per cent). For these same urines the Friedman test gave only 4 false positives. In ten of the thirty cases in which the pregnandiol test gave a false positive, no data on the clinical history were available; in twelve cases there was no amenorrhea; in six cases the menstrual cycle was irregular; one patient was lactating; and one had a corpus luteum cyst. It is evident that the pregnandiol test gives presumptive evidence of pregnancy only if the urine is obtained in a period of amenorrhea in women whose menstrual cycles are otherwise normal. If the cycle is longer than the usual twenty-eight days, late pregnandiol excretion is to be expected because of late ovulation.

The pregnandiol test was also employed in 105 patients with symptoms of threatened abortion in the early months of pregnancy. In 39 cases the pregnandiol test was negative when the patient was first seen or became negative during the period of observation, and abortion occurred in all but two of these cases. In 54 cases in which the pregnandiol test remained positive, abortion did not occur, but in twelve cases with positive pregnandiol tests, abortion did occur. The prognostic value of the qualitative pregnandiol test in threatened abortion is greatest in the first three months of pregnancy. After that time increasing placental function increases the output of pregnandiol and a quantitative test is necessary to determine if there is a diminished progesterone metabolism.

HARVEY B. MATTHEWS.

Riley, Gardner M., Smith, Marjorie H., and Brown, Pearl: The Rapid Rat Test for Pregnancy, *J. Clin. Endocrinol.* 8: 233, March, 1948.

The authors review reports in the literature on the rapid rat test for pregnancy. The test is based on the hyperemic response in the ovaries of immature rats as a result of the injection of pregnancy urine.

achieved in the biophysiochemical domain permits another possible explanation for the cause of toxemias of pregnancy. In normal pregnancy there exists a peculiar state of equilibrium differing fundamentally, but in a state of perfect adaptation, from the nonpregnant state. In the so-called toxemias there exists a singularly unstable neurovegetative glandular, ionic, and colloidal state of biophysiochemical balances.

The writer proposes a new term, *Gravid, psychosomatic unstable equilibrium*. Instead of the American Welfare Committee of Maternity's usually accepted classification, he proposes regrouping the toxemias as (a) convulsive; (2) comatose; (3) hemorrhagic; (4) bilateral cortical necrosis of the kidneys; and (5) pyelitis of pregnancy.

The author then concludes with considerable detail on the physicochemical findings of blood. These he attempts to use to show the great influence of the mind upon functional disturbances and morphological variations often seen in pregnancy. Another term used instead of toxemia is *Psycho-organic Imbalance*.
CLAIR E. FOLSOME.

Peet, Max M., Isberg, Emil M., and Bassett, Robert C.: *Toxemia Superimposed Upon Prepregnant Hypertension Treated by Splanchnicectomy*, Surg., Gynec. & Obst., 1948.

The authors present the histories of five patients with severe chronic hypertensive vascular disease complicating pregnancy. They state that the patients were also suffering from superimposed toxemia but this does not seem probable either from examination of the histories or from the duration of the pregnancies, all of which were five months or less. The patients received bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy. In two of these the results were excellent, normal blood pressure levels being achieved, living children obtained, and a persistent cure of the hypertension effected. In the remaining three the hypertension was not relieved during the pregnancy, although in one there has been a subsequent diminution in pressure.
L. M. HELLMAN.

This study indicates by bacteriologic findings that penicillin, when used as a single instillation, compares favorably with silver nitrate as a prophylactic agent. (41 per cent positive cultures after penicillin and 45 per cent positive cultures after silver nitrate.)

Further study is required for interpretation of the observed increase of the bacterial flora with time in the conjunctiva of the newborn infant. JAMES P. MARR.

Rutherford, Frederick W.: Recent Advances in Surgery of the Newborn and of Early Infancy, West. J. Surg., page 298, May, 1948.

Peculiar metabolic requirements and the high surgical incidence of embryonic malformations make the surgery of the newborn and the infant a distinct specialty. Cleft lip and palate is best repaired during the period of maximum immunity in the first few weeks of life. Surgical repair of the palate may be deferred for twelve months. Attention should be given to dentition, care being used to protect the unerupted teeth. Adequate speech training is a necessary counterpart to surgery.

Tracheo-esophageal fistula is suspected when choking, coughing, and gasping occur of the time of the first feeding. Adequate parenteral fluid is given, cyclopropane by intubation for anesthesia, and primary anastomosis is usually possible. Peptic ulcer, usually the duodenal type, is fairly common and hemorrhage or perforation demands immediate operation. Congenital hypertrophic pyloric stenosis should no longer be considered an indication for emergency surgery, but a few days spent in re-establishing the electrolyte, fluid, protein, and vitamin balance is time well spent. Congenital atresia of the intestine or colon is characterized by delayed vomiting, and Lipiodol x-ray, never barium, is helpful. Preoperative preparation with duodenal suction and postoperative feedings with fat-free protein milk hasten recovery. Several anomalies of the anus and rectum are readily diagnosed and usually lend themselves readily to surgical correction. Intussusception sometime presents difficulty in diagnosis, but the infant previously healthy who has sudden abdominal pain, bloody stool, and a palpable abdominal tumor demands immediate operation. Congenital atresia of the bile duct is suspected when jaundice is progressive. Umbilical eventration and congenital diaphragmatic hernia are major procedures which cannot long be delayed. WILLIAM BICKERS.

Toxemia

Garber, Stanley T., and Assali, N. S.: Toxemias of Pregnancy, An. brasil. de gynec. 25: 87-100, Feb., 1948.

The authors review 1,310 cases of toxemia of pregnancy treated at the Cincinnati General Hospital over a six-year period, 1940 to 1945 inclusive. They classify their cases as 680 mild cases of toxemia; 379 severe toxemias; 40 instances of eclampsia, and 211 cases of hypertensive disease in pregnancy. During this time interval, six years, 13,784 deliveries were performed in this hospital, thus giving an incidence of 10 per cent toxemias of pregnancy. There were four maternal deaths, three in the pre-eclamptic group (0.8 per cent), and one death among the 40 eclampsia cases (2.4 per cent). There were 130 infant deaths in the series, which included 41 premature and 46 term stillborn infants and 24 premature and 19 term neonatal deaths. There were fifteen abortions in the series. The infant mortality as uncorrected was found to be 9.8 per cent and the uncorrected maternal mortality rate was 0.3 per cent.

The treatment stressed rest, salt-poor diet, magnesium sulfate, hypertonic glucose solutions and veratrum viride along with forced fluids and proper sedation. Three tables are included. CLAIR E. FOLSOME.

Leon, Juan: Toxemia of Pregnancy, Anales del Servicio de Obstetricia del Hospital Cosme Argerich 1: 25-41, Dec., 1947.

The author, of Buenos Aires, does not subscribe to the theory that the so-called toxemias of pregnancy are due to toxic substances or are of ovular origin. He feels that the progress

Necrology

FRANKLIN S. NEWELL, A.B., M.D., professor emeritus of clinical obstetrics at Harvard Medical School, died on March 3, 1949, in Boston, at the age of 77 years. A native of Roxbury, Massachusetts, he received his B.A. in 1892, and an M.D. in 1896, both at Harvard. He became visiting obstetrician to the Boston Lying-In Hospital in 1899, and served until his retirement in 1931. Dr. Newell was appointed in 1897 as assistant professor of obstetrics and gynecology at Harvard and then became full professor in 1917, until his retirement in 1931.

A frequent contributor to the JOURNAL, Dr. Newell was co-author with Dr. Edward Reynolds of a textbook on "Practical Obstetrics." President of the American Gynecological Society in 1926, he was also a member of the Boston Obstetrical Society and other medical organizations.

HOWARD CANNING TAYLOR, PH.B., M.D., well-known gynecologist of New York City, died at his home March 27, 1949, at the age of 82 years. Born in Greenes Farms, Conn., he graduated at Yale in 1888 and from the College of Physicians and Surgeons of New York in 1891. Dr. Taylor was affiliated with the Roosevelt Hospital during his entire professional life, beginning as an intern, then as attending gynecologist, and finally as consultant. He was also a clinical professor at the College from which he graduated. A Fellow of the New York Obstetrical Society and the American Gynecological Society, he had served as president of both organizations. Dr. Taylor was a member for many years of the Advisory Editorial Board of this JOURNAL and on his retirement was succeeded by his son, now an Associate Editor.

Correspondence

Abdominal Cystoceleoplasty

To the Editor:

In his presidential address to the American Gynecological Society in 1912, Howard A. Kelly began, "According as we remember others, so those yet to come will remember us." With this in mind, I cannot refrain from calling attention to the fact that, in that year of 1912, Dr. William Mecklenberg Polk read a paper at a meeting of the American Gynecological Society, noted in the Society's Transactions (*American Journal of Obstetrics and Diseases of Women and Children*, vol. 66, page 639) entitled "Procidentia Uteri: Suprapubic Plication of Vagina and Conjoined Shortening of Uterosacral and Broad Ligaments." This address presented the same technique that Dr. Charles B. Marek publishes in your JOURNAL, February, 1949, on page 345.

In addition, in the September number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY of 1929, page 345, I published an article entitled, "Intra-abdominal Reefing of the Pubocervical Fascia (Modified Polk Operation) for the Cure of Cystocele," in which I sought to revive the then obsolete Polk operation, applying it to cases in which supravaginal hysterectomy or ventrofixation was employed.

In retrospect, I may say that I have again abandoned the operation because recurrence of cystocele eventually took place in a considerable number of cases.

ROBERT T. FRANK, M.D.

1035 PARK AVENUE
NEW YORK CITY
March 11, 1949

Item

First Mexican Congress of Gynecology and Obstetrics

May 22-May 28, 1949, Mexico City, Mexico

The Mexican Gynecological and Obstetrical Association and its Affiliated Societies have organized the First Mexican Congress of Gynecology and Obstetrics, which will take place in Mexico City from May 22 to May 28, 1949. The scientific papers will be presented in the "Justo Sierra" (U.N.E.S.C.O.) Auditorium of the Escuela Normal de Maestros, and the social reunions in the Hotel del Prado. There will also be visits to the hospitals and clinics of the city and there will be ceremonies at the Chapultepec Castle and the Palace of Fine Arts, etc.

Any further information will be furnished by the Secretary of the Congress, Dr. Carlos Guerrero, Marsella 11, Mexico City.

Man's most compelling instincts are self-preservation and reproduction. Man's continued presence on this planet is predicated on his ability to continue to exist and to reproduce his kind. It is evident that food in the broad sense is of primary importance to the individual and to the species; without nutrition life cannot continue; without continuity of life and reasonable health there can be no self-defense; without these two, reproduction of the species ceases. Food has played a primary role in the survival and development of man. Probably it is the most important factor in reproduction.

Ancient writings, including the Old Testament of the Bible, contain many instances of laws and admonitions concerning foods. However, these have a general application to a people or tribe, and there is a paucity of dietary advice to the pregnant woman. More information concerning nutrition and reproduction can be obtained from a study of the customs and taboos of the American Indians, the Eskimos, and the present-day tribes and races in Africa and the South Sea Islands.

However, some records of ancient writings survive. In Papyrus Ebers,⁵ circa 1500 B.C., a collection of bits and pieces of Egyptian folklore translated by H. Joachim, there are passages relating to the pregnant woman. "To produce milk, mix fragrant bread made from soured durra (a variety of millet) with the ground poppy plant and require the parturient to sit crosslegged while eating it." Another passage relates to the treatment of protracted labor by applying peppermint to the bare posterior of the parturient woman—*vis a tergo*, so to speak.

Hippocrates is credited with the statement that women should use a regimen of rather dry food, for, he said, food that is dry is more adapted to the softness of their flesh and less diluted drinks are better for the womb and for pregnancy. He also sagely remarked that foods and drinks that are not quite so good are to be preferred, if only they are more agreeable. If a pregnant woman eats suckling pigs, the fetus will have weak joints and will be subject to diseases of the joints. Constantine is quoted as having wisely recommended that any food which is not near at hand or easily procurable should not be mentioned in the presence of a pregnant woman. If her desire [for food] is kindled and unsatisfied, there is danger that the uterus may sink down.

One bit of advice attributed to ancient Rome is that the burden of the parturient woman will be dispelled before the onset of labor if at that time she has eaten the flesh of wolves or if a woman who has tasted wolves' flesh that day attends the birth. Shades of Romulus and Remus! If a woman has eaten young stork, ophthalmia is prevented, the eyes are made clear and the child even surpasses the mother. A mother who wishes her child to have black eyes should frequently eat mice.

Opinions concerning the nutritional value of milk varied. It was said to be the most nourishing of all liquids used as food, but oddly enough, it was supposed to cause teeth to decay and kidney stones to develop. Another saying advised that, if a pregnant woman greatly desires milk, it should be boiled with salt water and a little sugar and the scum removed before drinking. Galen advised that milk with honey drunk by the parturient causes the uterus to sink

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PRESIDENTIAL ADDRESS*

Nutrition and Human Reproduction: An Historical Review

ROBERT D. MUSSEY, M.D., ROCHESTER, MINN.

(From the Section on Obstetrics and Gynecology, Mayo Clinic)

I HAVE chosen for the subject of my address an historical review of nutrition and reproduction. With full realization that I cannot qualify as an historian, a physiologist, or a trained nutritionist, I venture to pass on to you certain fancies and facts relating to nutrition and reproduction. The early history of nutrition in pregnancy is sketchy and the opinions expressed relating to food and pregnancy are unscientific and in many instances undesirable or even harmful. However, the experience in practical nutrition derived from observation and the trial and error method has led to the scientific and practical phases of nutrition in general and their application to pregnancy which have been developed in the first half of this century.

At the outset it is in order to define the term "nutrition," which is described in Webster as "the sum of the processes by which an animal or plant absorbs, or takes in and utilizes, food substances." Nutrition in pregnancy in reality embraces all that is implied in the use of the term "reproduction," which includes fertilization, nourishment of the embryo, growth and development of the fetus, and, as a corollary, the fitness and health of the mother. Food requirements depend on age, sex, climate, physical activity, and racial food habits, and it becomes obvious that the requirements change in the course of pregnancy and lactation.

*Presented at the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 10, 1948.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

staining well, and spaced loosely over the field (Fig. 4). The villous capillaries and vessels show no engorgement, dilatation, or rupture.

At the line of demarcation the appearance abruptly changes. The villi are of much greater size, crowded, and show early necrosis with pyknosis or karyorrhexis of the nuclei. (Figs. 4, 5.) There is still sufficient intervillous circulation of maternal blood to permit dissemination of poisonous products of necrosis and autolysis of the infarcted tissue through the maternal circulation.

It is probable that histamine is formed from placental histidine at an earlier stage than guanidine, the latter probably resulting from breakdown of placental arginine at a later stage of autolysis. Histamine is productive of vascular damage, shock, and a marked increase in tone of the uterus, all outstanding in abruptio placentae, whereas guanidine may well be the cause of the eclamptic convulsions, since this is known to be one of the characteristic effects. The



Fig. 9.—Eclampsia, Case 44; higher power magnification of subacute, late "E" hemorrhagic infarction of placenta, showing enlarged crowded villi, necrosis, and greatly distended villous vessels.

capillaries and vessels of the villi in abruptio and eclampsia alike are much distended, engorged, and even ruptured (Figs. 5, 9). Hofbauer¹¹ produced hemorrhage and placental separation in animals by histamine injections and called attention to the similarity of histamine effects to clinical abruptio.

At a somewhat later stage (subacute) the area of hemorrhagic infarction appears more compact and firm (late "E," Fig. 6) the cut surface being smooth and shiny if held toward the light. On bending the strip of placenta, the area of hemorrhagic infarction, being compact and homogeneous due to fusion of the necrosing elements, does not bend with the strip. It is still dark in color, but if somewhat older, the color change in the hemoglobin imparts a brown color to the lesion, "D" type (Fig. 6).

As to the etiology of the hemorrhagic type of infarction, we formerly attributed the lesion to the trauma of fetal movements on the exposed placental veins, or to the cholesterol vascular change which may be seen microscopically in the lining of many of the fetal vessels. However, thromboses could not be definitely found adjacent to cholesterol deposits in the vessel lining, or at possible sites of trauma on the fetal surface of the placenta, hence these possible factors do not seem to supply the answer.

down gently. One suggestion of significance was that, if fresh milk is drunk after childbirth, it makes the breasts secrete more abundantly.

If partridge eggs are eaten, they produce fertility and an abundance of milk. After Juno ate wild lettuce she conceived her daughter, Hebe, although formerly she had been sterile. Lettuce was said to have the greatest nourishing power of all vegetables, cooling and soothing the stomach, stimulating appetite and elimination, and promoting sleep. This sounds like a modern radio plug!

According to Nixon, in the Chou Dynasty, 1155 B.C., pregnant women were warned to be careful in the selection of their food; that, among other foods, goat meat would produce a sickly child, turtle meat a child with a short neck, and, aptly enough, that donkey meat would cause the woman to go over time and have a difficult labor. Perhaps the author had been irked by a stubborn donkey.

The continued existence of man through the periods of Greek and Roman ascendancy and the Dark Ages indicates that a diet sufficient for survival and reproduction must have been known and available during these times, although only meager writings on diet in pregnancy are extant. In *Priests of Lucina*, Findley quoted Albertus Magnus, a friar of the thirteenth century, who cautioned against mentioning injurious foods in the presence of the pregnant woman, for to deny her any food she may desire might cause the unborn child to die of weakness. In a treatise by Pratis, kindly translated from the Latin for me by Dr. John Miner, Constantine is said to have made a somewhat similar statement. In the *Rosengarten* of Eucharius Rösslin, A.D. 1513, there are colored drawings of the development and position of the fetus and its delivery but no mention is made of diet.

In 1767, Zückert wrote a treatise devoted almost exclusively to dietary advice to the pregnant woman. In this occurs the first mention I have found of avoidance of salt, contained in his admonition to pregnant women to avoid salty, acrid, sour foods, eggs, and all greasy foods that have stood long in copper kettles. It is noteworthy that he does not forbid digestible meat. In the matter of diet he divided pregnant women into three groups: 1. The peasant class who were healthy and strong on a diet of pumpernickel (bread made of coarse rye), ammunition bread (also a dry black bread for troops in the field), cheese and tough meat. He stated that this food agreed with these women because of good digestion derived from simple living and physical work. 2. Those women of a more leisurely group, "commonly city dwellers and those in the upper classes with weakly bodies and stomachs, tender sensitive nerves who commonly eat anything their appetite demands." 3. Women with aversion to food or those with gastritis and atonic stomachs. He recommended common bread (no doubt made with whole grain), greens, and simply prepared foods, and agreed with the free choice of other eatables, except harmful foods; he urged moderation in eating. He wisely remarked, "It is a great pity [that moderation] does not please those who concede absolute power to their senses." Pregnant women "who eat well and digest much are plethoric and this is the more dangerous to pregnant women who have no work and exercise." He advised the pregnant woman to "eat little and not late." He warned against the extensive use of tea or coffee because too much warm fluid relaxed and softened the stomach and intestines, which "become

like the withered skin of the hand of the laundress." Surprisingly enough, for those times, he lauded plain water, calling it "the sacred drink of the ancient patriarchs," but he warned, "water chills and burdens stomachs unaccustomed to it." Although he said milk was advisable for women with good stomachs, he recommended beer, asserting that beer has more power than merely to quench thirst, thin the blood, and strengthen the body; and he stated, "no one will persuade the world that a glass of good, pure wine has hurt anybody when taken in moderation." Coming into modern times, Drummond, quoted by Nixon, stated that malnutrition was more rife in England in the beginning of the present century than in medieval times.

It is known that even prior to 1850 the diet of some pregnant women was being restricted in order to lessen the size of the fetus, for Cazeaux, in his treatise on midwifery of that date, stated that he did not agree with this recommendation. Naegele, in 1853, advised two rules for pregnant women, first that small, frequent meals were better than one or two large, protracted meals, and second, that salty, spicy, sour foods should be avoided. In the nineteenth century and even in early years of the twentieth, it was more or less customary for recently delivered women to be placed for a day or two on very limited diets similar to those given to patients after laparotomy. Atkinson, in 1879, wrote that this was not sound reasoning and that the diet of the recently delivered woman should be guided by her appetite and her general condition. Burnett, of London, England, also was in advance of his time when in 1880 he wrote on the prevention of harelip, cleft palate, and other congenital defects by medicinal and nutritional treatment of the mother during pregnancy. A keen observer, he stated with outspoken expression and vigorous criticism, "The child of the well-fed, well-worked, cheerful, happy woman living in a sunlit, airy habitation, is at birth the finest specimen of its kind. On the other hand, what a miserable sight do the newborn babies of our courts and alleys, and of the pampered, tight-laced, high-heeled, lazy, lounging, carriage-possessing women of the high classes present: The extremes meet, the poor, blanched creature, half-starved, over-worked, shut in some close sunless dwelling brings forth her fruit very like that of the pale-faced, over-fed, under-worked, sofa-loving sister of the mansion and of the palace."

It is evident that all was not well with the dietary habits of the general population and incidentally of pregnant women in Europe in the so-called era of growing enlightenment of the eighteenth and nineteenth centuries. Life in the towns and cities had become more sheltered and many people had forgotten much of the knowledge of what to eat and what not to eat—food habits, if you like, acquired by primitive people in their keen and continuous struggle for survival. Much has been learned from century-old taboos and customs of primitive people which are being followed today among tribes in Africa and the South Sea Islands and among certain groups of Eskimos and natives of South America. The Eskimos on their natural diet of fish, seal oil and meat, animal organs, moss and roots and bulbs of water plants, maintained normal health, normal bony development, and normal teeth, but with the advent of highly milled flour, polished rice, and the canned foods of civilization their general health was lowered and dental caries and pyorrhea became evident.

In the course of his investigation of the nutritional factors associated with the development and maintenance of the teeth, Price found that most of the primitive tribes had evolved a balanced diet, containing adequate calories, a proper balance between proteins, fats, and carbohydrates, and sufficient vitamins and minerals. He noted that among the Masai, a hunting tribe of East Africa, each child and pregnant woman received daily a special ration of blood, along with milk and meat. A neighboring tribe, the Kikuyu, an agricultural people, had a special diet for women during pregnancy and lactation, consisting of sweet potatoes, corn, beans, bananas and kaffir, a variety of millet. Many of these people attained advanced years without dental decay, pyorrhea, or the loss of teeth.

Most of the tribes among the American Indians lived on wild game, chiefly the internal organs and bone marrow, with maize and some vegetables and, in winter, the bark and buds of trees; much of the muscle meat was fed to dogs. Among some Indian tribes it was customary for the husband to go on a five-day fast after his child was born. This may have been done to permit his squaw to have more food in times of scarcity. With the advent of the reservation life and the benefits of modern civilization and its food there was a decided decrease in normal births and an increase in neonatal mortality rate. However, in recent years, with the adoption of the newer scientific knowledge of dietary requirements, improvement has occurred.

Diets vary in different localities, depending on climate, topography, and availability of dietary essentials; for example, in isolated Swiss valleys an almost normal diet is maintained on whole rye bread, dairy products, various fresh vegetables in season, stored vegetables in winter, and meat once a week. However, the lack of iodine in the ground water and drinking water in many localities resulted in endemic colloid goiter; under these conditions pregnant women often gave birth to cretins. Dental caries is notoriously common among the urban Scots and yet in the islands of the outer Hebrides there is little dental caries; the food consists of oat products, a few green vegetables and sea foods, including fish livers, a meager but balanced diet.

In China, bones boiled in dilute acids until they were soft were a dietary delicacy, no doubt owing to the prevalent lack of calcium and phosphorus; this lack no doubt inspired the gift of pigs' feet to the expectant mother. The Lapps remain well on a meager diet when it is supplemented by two or three ounces of fish oil daily. Among our early pioneers, pushing westward through the Middle Western states, pregnant women and children became ill and many died from "milk sickness," as did the cattle which ate richweed or white snake root.

Approximately fifty years ago a controversy over maternal nutrition and its effect on the size of the fetus arose among obstetricians, which awakened interest in maternal diets. In an ambitious attempt to reduce the weight of the baby and in particular the size and consistency of the fetal head, Prochownik³⁵ in the eighties of the last century carried thirty-one patients through thirty-six pregnancies, during the last six weeks of which their diet consisted of an increased amount of protein with a decided decrease in carbohydrates and fluids. He did not claim to reduce the size of fetal bones or retard ossification but to

reduce fat tissue, resulting in thinness and slackness of the subcutaneous tissues of the skin covering the head, which, he said, increased mobility of skull bones against each other and facilitated moulding.

As a result of sheer persistence and assertive publications, Prochownick^{34, 35} extended the use of this diet, which I previously mentioned as having been rejected by Cazeaux in 1850, until it became known as the "Prochownick diet." In the course of the ensuing thirty or more years there was much controversy among the medical profession, obstetricians in particular, relative to the effect of this diet on the fetus and to its relief of dystocia. Lahmann, in 1893, advised a dry diet, with a minimum of salt and with limited calories, which he said produced smaller babies, fewer operative procedures, and less fetal injury. Later many well-known obstetricians, for example, Williams,⁵¹ Cragin (quoted by Padlock), Hirst (quoted by Paton), Slemmons, Edgar, Cornell, Rucker, and others, went into print with statements in favor of Prochownick's claims, while Reed (quoted by Oldham), Landau, Ehrenfest, and others opposed them. Ahlfeld (quoted by Oldham) agreed with Baumm that growth and development of the fetus in utero are influenced only by race and constitution of both parents, by heredity, and by the sex of the fetus, unless the diet is totally inadequate. However, opinion remained divided concerning the practical value of attempting to reduce the weight of the fetus by reducing the maternal diet; the possible importance of fetal weight reduction has waned since increased accuracy of roentgenologic pelvimetry and improvement in the technique of cesarean section have solved the problem of dystocia in most instances.

Among the early writers, Paton, in 1903, Murlin, in 1917, and Ehrenfest, in 1919, gave clear and searching analyses of the then known effect of nutrition on maternal health, labor, and the fetus. These writings and many other factors contributed to stimulate research in nutrition in the twentieth century.

A vast amount of thought and research has been devoted to nutrition in its relationship to reproduction. It is evident that we are too close to much of the investigation relating to this subject to evaluate its historical significance accurately. To attempt to enumerate all of the many excellent articles and research projects would place us in the position of the explorer who could not see the beauty of the woods because of the trees around him. It would be premature even to try to evaluate all of the findings and claims of various workers. Nor shall I attempt to give a chronologic description of the results of these investigations, but rather to present, as nearly as possible, the present-day consensus of investigators, nutritionists, and obstetricians concerning the relationship of food and its various elements to the well-being of the mother and the normal development and health of the fetus.

Our interest centers on the dietary requirements of the pregnant woman and her fetus. In this consideration of the immediate dietary requirements of the pregnant woman it must be borne in mind that the diet of a given generation may affect the offspring several generations hence. In other words, a woman may remain well on a diet which will prove to be inadequate under the added physiologic demands of pregnancy so that her offspring may suffer in development and in capacity to reproduce their normal kind.

I shall refrain from discussing the fetal-maternal relationship and the pertinent question first asked by Harvey: Does the placenta act by digestion or in a purely mechanical manner? Adequate exposition of this question is not feasible at this time. It may be stated that the initial period of pregnancy is one of parasitism. However, the nutrition of the fetus is not all obtained by simple diffusion, supporting the idea of active selective absorptive properties on the part of the placenta.

It is well known that the constituents of food are protein, fat, carbohydrate, water, minerals—including calcium, phosphorus, magnesium, iron and iodine—and vitamins—including fat-soluble A, D, and E, and water-soluble B-complex and C. Protein is the most important ingredient of food because it is the basic material for building tissue; fat is especially necessary as a solvent of vitamins A, D, and E; carbohydrates furnish most of the total calories and are the most readily accessible fuel for heat and energy production.

The nutritional requirements of an individual pregnant woman depend on heredity, environment, previous status of nutrition, weight, stage of pregnancy, and physical activity. It may be said that a pregnant woman's nutritional requirements are the same qualitatively as those of the nonpregnant, but that she requires more of everything, particularly protein, calcium, phosphorus, iron, iodine, and the vitamins. Too often her increased appetite has been satisfied by increased consumption of carbohydrates. Contrary to the opinion which prevailed as recently as two or three decades ago, that protein foods should be restricted during pregnancy, it is now held that the protein intake, which is at least 60 Gm. daily for the average woman, should be increased during pregnancy to a minimum of approximately 90 Gm. daily. There should be sufficient fat in the diet to act as a carrier of vitamins A and D and sufficient carbohydrates to reinforce the calories obtained from protein in order to produce energy and maintain proper weight.

McCarrison has pointed out that the Commission of the League of Nations advises the proportion of animal to vegetable protein as approximately 3 to 2. Animal protein includes that obtainable from meat, eggs, sea food, poultry, milk and cheese, while vegetable protein is furnished by legumes, other vegetables, bread and cereals. Certain proteins, namely beef, eggs, lactalbumin, and the glutenin of wheat, contain all of the essential amino acids. Milk appears to be a stabilizing factor in the human diet in civilized countries.

As amino acids, protein passes through the placenta by diffusion, but the fetal plasma at term has a higher percentage of amino acid nitrogen than the mother's plasma, suggesting a fixation method in the fetus which may control retention by the fetus of the amino acids. Ordinarily adequate maternal diet permits the storage of nitrogen, which begins as early as the tenth week of pregnancy and marks the state of positive nitrogen balance.

In 1933 Mellanby suggested that toxemias of pregnancy may be caused by inadequate diets, particularly of proteins and vitamins. Strauss stated that some toxemias could be traced to an inadequate intake of protein over a number of years. Protein calories need not exceed 10 per cent of the total calories, except under certain environmental and racial conditions, for example, in the

case of the Eskimos, who may consume 250 to 300 Gm. of protein daily. Ninety grams of protein are insufficient to meet the daily caloric requirement and the remainder is furnished by fat and carbohydrate food. Carbohydrates, about 250 Gm. of which are consumed daily, are protein-savers and furnish 50 to 60 per cent of the daily caloric intake. The amount of carbohydrate ingested needs control, because its excessive use results in undue storage of fat in the body tissues.

Fats ordinarily provide 35 per cent of the calories of the normal diet, furnishing about 100 to 140 Gm. daily. Fats are an additional source of energy, but their major role is to assist in the utilization of calcium and phosphorus and the fat-soluble vitamins, A, D, E and K. The maternal blood has a higher lipid content than the fetal blood. The appetite for food is increased among pregnant women and there is a still greater demand among lactating women. The storage of nitrogen in a pregnant woman, in addition to forming reserve for nitrogen loss, increases her ability to lactate. Voluntary consumption of food may be 60 per cent greater among lactating women than during pregnancy.

The story of calcium is opened by the significant need for an adequate maternal storage of calcium. The fetus demands and gets calcium from the mother even if her diet is deficient; therefore, the prevention of calcium deficiency in the newborn is a problem for the obstetrician to solve by prenatal dietary measures. Phosphorus and calcium go together as the Damon and Pythias of diet. Phosphorus, as well as calcium, is activated by vitamin D and sunlight and is essential in the laying down of the bony framework and dental foundation in the fetus. It is claimed that a high mineral diet appears to be of value in developing relative immunity of the fetus to infection.

Iodine is concerned with metabolism and the maintenance of cell structure; its richest source is in sea food and in vegetables grown near the seashore. Its deficiency in the maternal diet is associated with the production of colloid goiter in the mother and of colloid goiter and, in cases in which the deficiency is extreme, with cretinism in the fetus.

Ingestion of iron is important. The pregnant woman has a relative anemia owing to blood dilution resulting from 20 per cent increase in blood volume. It is important that an iron deficiency or hypochromic anemia does not develop during pregnancy because of its effect on maternal health and for fear a similar delayed anemia will develop in the infant from the age of 2 to 6 months. An iron deficiency may develop as a result of protein deficiency. To avoid this type of maternal anemia the pregnant woman's minimal diet should contain approximately 90 Gm. of protein daily, plus adequate liver, and, when possible, such foods as apricots, egg yolk, cooked mustard greens, oysters, green vegetables, prunes, peaches, pineapple, orange and grapefruit.

Water Balance

It has been suggested that 1.0 c.c. of water should be ingested for each food calorie. Aside from the water in food, this would require seven to eight glasses daily; approximately 2 quarts of fluid are dispersed from the skin and lungs and alimentary tract and 1½ quarts by the kidneys. A positive water balance ob-

tains in pregnancy and normally about 10 pounds of the gain of weight in pregnancy are owing to this water retention. Slemons has shown that the urinary output of the adult male represents 90 per cent of the fluid intake, primiparas voided 72 per cent of fluid drunk, multiparas 48 per cent, and multiparas with the fetus dead in utero voided an average of 93 per cent of the fluid drunk. Impaired excretion of sodium causes undue water retention and this appears to be a factor in the etiology of toxemia. For this reason a low salt diet is advised.

Vitamins

The role of the vitamins in nutrition, now well known, is so broadly advertised "across the land," that, to paraphrase an old saying, he who speeds may read. We are advised to take vitamins to prevent this or that or to cure the other. Nutritionists state that a balanced adequate diet furnishes sufficient vitamins for the average person. However, in no other field of nutrition is the value of vitamins so clearly shown as in pregnancy. Researches have revealed various vitamins as the cause of diseases which baffled physicians and investigators for many years; lack of sufficient vitamin C as the cause of scurvy, deficiency of vitamin D and its accompanying minerals, calcium and phosphorus, in rickets and osteomalacia, deficiency of vitamin B in beriberi, of B-complex in pellagra, of vitamin A in night blindness and of vitamin E in sterility in rats. Sherman^{39, 40} has stated that lack of vitamin E in male rats produces sterility and eventually leads to destruction of germ cells. Shute⁴¹⁻⁴³ has stated that lack of vitamin E is a factor in abortion and abruptio placentae.

Among the vitamins, A is essential to reproduction and fetal growth and its maternal lack is related to deficiency diseases and perhaps lowers immunity to infection, predisposing to puerperal sepsis. McCollum has stated that the supplementary administration of vitamin A tends to decrease the severity and frequency of colds. A vitamin A level sufficient for maternal health may, however, result in disaster for the offspring; for example, the teeth of the mother are less affected than those of the offspring. Vitamin A is inactivated by rancidity, by exposure to ultraviolet irradiation and to heat in the presence of oxygen. Carotene and vitamin A are poorly absorbed from the intestine whenever fat absorption is defective and in the presence of mineral oil laxatives.

Vitamin B is frequently lacking in the diet of American women, its lack in prenatal diet being evidenced by anemia, anorexia, irritability, and emotional instability, and in the presence of more severe deficiencies, by beriberi or by pellagra. A mother who has latent beriberi may bear a child who has congenital malformations. It has been shown that rats with riboflavin (B₂) deficiency may have repeated pregnancies resulting in severe fetal malformations. The synthesis of B vitamins by intestinal bacteria has a vital role in man and animals but in man supplementary dietary intake of B vitamins is necessary. The bacterial synthesis in the bowel may be suppressed by the administration of drugs, such as the sulfonamides, particularly when the therapy is protracted. Vitamin B is abundant in many foods, particularly meat, milk, and eggs. In the presence of known or suspected B deficiency the diet may be supplemented by yeast, yeast concentrates, and wheat germ. It was not until recently that the re-

searches of Warkany and others emphasized the importance of a reasonably adequate protein content as well as certain vitamins, particularly A and B, in the normal development of the fetus in rats. Warkany has stated that the organogenesis of the human embryo is practically finished at ten weeks after conception, whereas nutritional supplements usually are not given until the latter half of pregnancy.

There is a widespread belief among laymen and many physicians that systemic and multiple congenital malformations are always the result of defective germ plasm which is genetically determined or hereditary. Perhaps a nutritional deficiency resulting in a defective gene leads to the same congenital abnormality.

Ascorbic acid (vitamin C) is recognized to be decidedly important to normal reproduction. It is, of course, well known that it occurs abundantly in citrus fruit and tomatoes. The fetus has the faculty of taking its needed vitamin C from the maternal circulation, so that vitamin C in the maternal plasma may be lower than in the cord blood. A decidedly low level of ascorbic acid in maternal plasma within the range of clinical scurvy has been noted in severe cases of hyperemesis. Tompkins has remarked that the vitamin C content is low in artificially ripened citrus fruit picked green for shipping purposes.

I have stated previously that normal reproduction requires adequate amounts of protein in the diet, that the ingestion of protein should be increased during pregnancy, particularly in its latter half, and that there should be a still greater increase of protein in the diet of the lactating woman. This statement is made advisedly because authorities on nutrition agree that protein is the most important component of the diet during pregnancy. A protein-poor diet is a common fault among pregnant women. Burke's statement is borne out by Williams,⁵⁰ Tompkins,⁴⁸ and many others, that malnutrition of protein and other substances in pregnancy results in a lower average hemoglobin and serum protein, a higher incidence of pre-eclampsia, a strikingly higher incidence of edema, increased maternal morbidity, and an increased fetal mortality rate. The observations of Theobald^{46, 47} on the role of calcium, iron, and iodine, of De Snoo on salt as a prime factor in the production of pre-eclampsia, of Strauss, and many others well merit careful study.

Normal increase of weight during pregnancy amounts to 14 to 20 per cent of the pregravid weight. This is owing largely to an increase of body nitrogen and fat, retention of water, including increased blood volume, tissue fluid retention, and amniotic fluid. The pregnant woman stores nitrogen in the uterus and other tissues as a reserve against nitrogen depletion in the course of labor and lactation.

It appears that excessive gain of weight during pregnancy is owing to undue retention of fluid in the tissues and often to the excessive storage of body fat. Time does not permit full discussion of the causes of edema during pregnancy, including increased intracapillary pressure, lowered serum proteins and undue retention of the sodium ion. The prenatal diet often is too high in carbohydrates and various sodium salts and too low in protein, vitamins, and alkaline minerals.

When hypoproteinemia is present, signs of toxemia have been produced by feeding various sodium salts. In the absence of hypoproteinemia, the feeding of sodium salts did not produce symptoms of toxemia.

Time does not permit me to continue with an extended description of the various disturbances of the reproductive function resulting from diets inadequate or deficient in various essential foods, minerals, and vitamins. I have already mentioned many of these nutritional diseases and complications. Perhaps the most notable reports of historical significance in the field of nutrition as related to reproduction have been the work of Warkany and others on the effect of various maternal and sometimes paternal nutritional deficiencies on the fetus of the rat and larger mammals, varying from resorption, stillbirths, and neonatal deaths, to bony malformations. Paralleling this work on rats, Burke found an amazingly large percentage of inadequate prenatal diets among the mothers of more than 200 infants, including stillborn infants, neonatal deaths, premature and functionally immature infants, and those with marked congenital defects. These and other research work demonstrate that adequate nutrition for women during pregnancy is an important factor in lowering the incidence of stillbirths and neonatal deaths.

In conclusion, I wish to repeat Burke's statement that there can be little doubt that adequate nutrition of the pregnant woman is sufficiently important to the normal growth and development of the fetus and the health of the mother to warrant a place in all prenatal care programs. "If a good diet is a safety factor to the mother in the prevention of certain forms of toxemia, that alone is important."

In this brief review of certain historical references and the present-day status of nutrition and reproduction, I have departed from the usual philosophical address given by presidents of this body. We have traveled through many centuries to learn something of the fancies and fallacies and, finally, of the present-day facts of nutrition and its possible relationship to human reproduction.

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Spanner's investigations of the placental circulation disclosed certain characteristics of the placental veins which are extremely significant. He demonstrated the *presence of sphincters* in the collecting veins of the placenta as shown in Figs. 10, 11, taken from his publication.⁹

Just what physiological purpose the sphincters serve is not known, but they would seem to insure a more stable content of blood in the villous vessels and to counteract the tendency of uterine contractions to overload the umbilical vein and the fetal heart.

If, however, the sphincters are susceptible to spasmogenic influences originating in pituitary (?) or renal (?) secretions, whether overproduced or insufficiently held in abeyance, the effect upon the dependent villi would be to produce an appearance identical with that which has previously been described in the acute or subacute hemorrhagic infarcts.

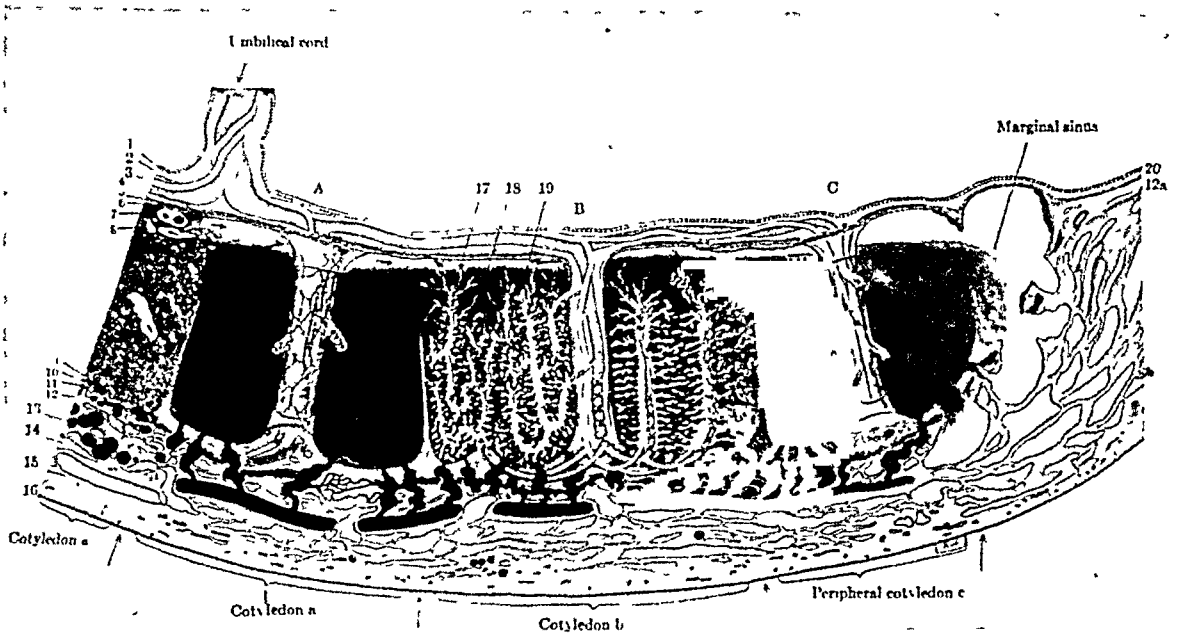


Fig. 10.—Spanner's "Diagram of the Placental Circulation at Term," showing sphincters in main and subsidiary collecting veins of the placenta. Arrangement of veins probably determines form and extent of hemorrhagic infarction (see Figs. 2 and 3). (From DeLee-Greenhill: *Obstetrics*.)

Spasm of the sphincters of the vein serving a unit of placental tissue would at once prevent escape of blood from the unit of dependent villi. The fetal heart, continuing to force blood into this unit through a branch of the umbilical artery, causes the villous vessels to become engorged and distended (Figs. 5, 8, 9). With stoppage of circulation in the vessels, thrombosis follows and the villi become necrotic (Fig. 8). The infarction outlines the pattern of the circulation serving this unit of placental tissue and demarcation is very sharp (Figs. 3, 4). It distinctly places the circulatory disturbance on the fetal and not on the maternal side.

Intrauterine fetal death is followed by maceration of the fetus but is not followed by maceration of the placenta. The cells stain well, the villous vessels show no engorgement or distention, and the villi are of normal size. The inference is that the intervillous maternal circulation is apparently sufficient to preserve temporarily the vitality of the villi and there is no immediate necrosis and toxemia.

However, if there is obstruction to the outflow of blood from the villi through the collecting vein, the resulting distention, engorgement, and thrombo-

As a result of tremendous advances in the study of the life process through the tools of chemistry, physics, and physiology, we have learned to conceive of man as an animal organism constantly interacting with his physical environment, striving to maintain a harmonious balance of physiological and chemical activity. At the same time we have learned that he is a social organism as well, constantly interacting with other units of the social system of which he is a part. We know also that the momentum of technological change has increased tremendously during the past century, in medicine as in other areas of our society. It is not strange that, in the social process of adaptation to meet revolutionary changes in the production and distribution of goods and in communication and transportation, we are faced with recurring economic and social crises. Only to the extent that society can adapt itself to the constantly changing demands of our technological age will it be reasonable to expect all men to find a degree of happiness.

Increasingly, medicine is focusing its attention on man as a social organism. The realization is growing that, while there are volumes yet to be learned about the physical aspects of man in health and in disease, the great contributions of the future will spring from an understanding of those subtle functions and forces which determine man's reaction as an individual in a social organization. Justice Holmes put it more succinctly when he wrote: "Man, whether he realizes it or not, is always fighting for the kind of a world he wants." The challenge of the future lies in man's constant struggle, consciously and unconsciously, to find happiness in a changing world, a world that is constantly making new and greater demands on both society and on the individual. This challenge goes very deep indeed to the very roots of the problem of man's survival on earth. Medicine is concerned with the preservation of life, with man's survival in this complex and ever-changing world. Perhaps no other group of professional men is more concerned with this whole problem than this Association.

As I have suggested, we are increasingly interested in the social aspects of life and living. Our primary concern always has been and always will be the individual and his health. But today the individual human being is caught up in forces far beyond his own personal control. Perhaps the most important single fact with which all of us are faced—particularly American leaders in the professions, in business, and in government—is the stark fact that the world's population is increasing faster than man's capacity to supply all his basic needs. Despite the loss of millions of people directly and indirectly because of the war, the world's population has continued to increase to a present total of approximately two billion, one hundred fifty million people. At the time of the American Revolution the population of the world totalled some six hundred thirty million, less than a third of the present figure. In our own country the population has almost doubled since 1900, increasing from seventy-five million to approximately one hundred forty-four million people. Increasing attention is and must be given to the problem of making the resources of the earth provide means of subsistence for this ever-growing population. It has been taken for

MEDICINE'S RESPONSE TO THE CHALLENGE OF OUR TIME*

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DRAMATIC indeed have been recent accomplishments in the specialties of obstetrics and gynecology. There has been a gratifying decrease in the maternal death rate largely due, perhaps, to better prenatal care, conservative obstetric procedures, and the advent of chemotherapy and antibiotic treatment generally. Since my days of practice one of the most interesting developments is the discovery of the Rh factor in blood compatibility and the application of this knowledge in blood transfusions and in an understanding of the pathogenesis of fetal erythroblastosis. Investigations of dietary deficiencies which have been carried on for many years are finding new applications. This is true also, I am told, of complications of pregnancy such as anemias and toxemias and in the correction of mineral and vitamin deficiencies affecting the mother and the fetus. In the field of gynecological surgery, we note the description of new surgical techniques in general and cesarean sections in particular. Renewed interest in such procedures as the Wertheim operation for cancer of the uterine corpus indicates that definite progress is being made. Progress in cancer studies generally is accelerating and a better understanding of this histochemical process is coming to light which will benefit mankind through the clinical specialties.

As the problems of medicine are pursued to their fundamentals, it is interesting to observe that they are all grounded in the natural sciences as they apply to the life process. It is on this firm base of scientific knowledge that all our medical specialties rest. Our specialties of medicine, for a time somewhat isolated from one another, are gradually drawing closer together. This process has been speeded as we have increased our knowledge of the inter-relations between various parts of the body.

It is encouraging indeed to note the renewed emphasis your specialties place on the importance of research in education and training.

It is sometimes difficult to see the full drama of the development of modern medicine in the perspective of history. We should remember that only some forty generations of fifty years each have elapsed since Hippocrates lived and only two or three since the development of modern medicine as we know it began to take form. Only in the twentieth century, for instance, has medical science been able to minimize the ravages of war by reducing the morbidity of epidemic disease and nonbattle casualties below that of battle casualties. During World War II important advances were made in the cure of battle casualties as well.

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Planned parenthood, as a partial answer to this problem, will naturally command our special interest. We have a special obligation, I think, to encourage educational opportunities for millions of underprivileged people and thus aid in controlling population growth where it needs control. The United Nations, UNESCO, and the World Health Organization offer the possibility of developing world-wide programs along these lines that can materially affect the course of contemporary civilization. All that has been accomplished since the war in bringing relief and reconstruction to war-torn countries is a mere buying of time in which to solve the greater problem of the total adjustment of mankind to his total physical and social world.

Economic and political systems which help to alleviate the acute symptoms of the day will not cure the chronic social and economic disorders that have grown out of man's quest for the means of survival. Most of the wars of history have arisen from the basic needs of people for expanded land areas for the production of food, fiber, and shelter. The wars of this century have risen to cataclysmic force. In another war, our population problem may be solved simply and in a relatively short time. Whether the survivors can make any kind of satisfactory adjustment to their earth is something no one can predict. But, through modern science and technology, the intelligent use of all media of communication, by education, by good will and cooperation, man can, if he will, arrest the downward spiral of our civilization. This task places great responsibility upon the American medical profession, holding leadership as it does among the medical professions of all nations and dedicated as it is to the health and welfare of mankind. Ours must be a response that will aid all men of good will to seek solutions to the major problems of survival which face mankind.

Is this not the crisis and struggle of our time? Are there not too many people who have little or no respect for their fellow men—too many people who seek only to gratify their own selfish and acquisitive instincts? What a tragedy this is when probably, surely, there is enough for everyone's need but, as someone recently remarked, not enough for everyone's greed. The physician, like the philosopher and the saint, puts down this sorry scheme of things as man's baser nature and, with patience, kindness, and tolerance, goes about his work of healing and prays that time will not run out. As we look back across the years of man's struggle and despair and forward to the better times we may have if we but will, we must see to it that, centuries from now, men will look back and say of us that we built upon the best that was in us and fashioned a better world for them. Medicine, with its age-old concern for the sick, the poor as well as the rich, the weak as well as the strong, has been an influence for good surpassed only by the moral precepts of religion. The services of medicine, like those of religion, have been largely personal. Medicine of the future must progress as a social, as well as biological, science and must broaden its outlook accordingly. Medicine is coming of age as a social science in the service of mankind and of his society. This must be medicine's response to the challenge of our times.

granted that the resources of the earth are limitless, and that they can endlessly supply the needs of an ever-growing world population. Serious studies have shown, however, that the material resources of the earth have been seriously depleted in many areas. Such a depletion of resources has spelled the end of civilizations of the past.

Physicians always have known that man is part of his physical environment, that he definitely depends upon it for his survival, and that he is equally dependent upon his fellow human beings in a society of which all men are essential elements. Concerned as we are with the welfare of the individual man and woman, we must also do our part as medical men in solving the problem of mankind's adjustment to its environment and to the resources of the earth. Only in our generation have science and technology begun to address themselves to the problems created by man's impoverishment and looting of the earth.

We have learned painfully, for example, that to mine the hills of their forests without making provision for their replacement not only robs us of a resource but also creates abnormal conditions which lead to floods and destruction. The science of forestry is teaching a new program of perpetual yield of timber crops which preserves not only timber but the soils and their wealth as well. Likewise, agriculture is preserving the wealth of the soil through better planned farming which will give a perpetual yield of crops.

Whether man can correct the damage already done to his material means of subsistence in time to stay the deterioration of present world civilization is one of the real crises of our times. The solution of this problem is basic to the whole problem of war and peace today, tomorrow, and next year, and in generations to come. As Americans, we are particularly fortunate because of the great, though not unlimited, resources of our nation. Compared with other parts of the world, ours is abundance indeed, but we cannot ignore the basic problems faced by mankind elsewhere. We have learned at great cost that this is one world or it is none, even though we know painfully that today we live in two worlds not of our choosing. We know that the world will one day be united again, either by peaceful or by warlike means. The basic problem, however, will still remain: that is, how man can harmoniously adjust himself to the world in which he finds himself and to its resources for supporting him?

What will be man's response to his responsibility for the future of mankind?

I suggest that medicine's response to the challenge of our times is a vital and most important one. Fundamentally, medicine is concerned with the preservation and nurture of mankind. While we must continue to serve individual human beings with all our knowledge and our skill, more than this we must, along with other leaders of our communities, join in every serious effort to make a more satisfactory adjustment of man to his world. This involves such practical pursuits as aiding in all conservation programs, supporting educational and research activities which will provide the know-how and the skilled personnel in scientific and technological fields necessary to conserve and develop the resources of depleted parts of the earth.

carefully considered, and I hope it will both carry weight and invite verification. May I say that, in order to exclude any personal favor, the results have been assessed and tabulated by an independent observer. With few exceptions the operations were performed in Sir Patrick Dun's Hospital, Dublin, where I was Gynaecologist for twelve years prior to my appointment to the Rotunda.

The Material Under Review

The clinical material upon which this paper is based concerns 113 young, and otherwise healthy, women whose dysmenorrhea was considered *primary* and to be so severe that they were unable to live normal lives, being incapacitated to a serious degree each month. The review covers the years 1936 to 1945, and in 1945 the 113 women who had been treated by some form of nerve division were written to in order to "follow up" the results. No contact was established with 31, but there were 82 replies. Unfortunately, the details of a further 24 cases were lost and these are not included.

I will now consider the 82 cases of dysmenorrhea from which replies were received. The treatment was as follows:

- 21 Ovarian denervations.
- 34 Presacral sympathectomies.
- 27 Combined ovarian and uterine denervations.

It is first necessary to state the criteria from which I believe it possible to make a differential diagnosis of the source of primary dysmenorrhea.

The Differential Diagnosis of Ovarian From Uterine Pain

The most obvious method of discovering if the menstrual pain is of ovarian origin is to apply reasonably firm bimanual compression to the ovary while asking if the pain or discomfort thus produced is similar to that experienced at the menstrual times (the viscerosensory reflex). If so, this would be a reasonable indication of the origin of the pain, of the discomfort, and of the nausea. But in many the discomfort thus produced does not resemble the menstrual pain, and it is then possibly of uterine origin. The "sound test" I have already described elsewhere is of the utmost importance in establishing a correct diagnosis.

The Sound Test.—The passing of a sterile uterine sound, either by touch or by sight, is usually easy and, in my experience, has never been followed by immediate or remote ill effects. All precautions should be taken to exclude pregnancy, cervical infection, or other contraindication, before the sound is passed. In several of my early cases a small intrauterine bag was inserted into the uterus, with full aseptic precautions, and was inflated to 5 c.c. capacity, to test for uterine pain. In others, when the Fallopian tubes were blocked, Rubin's apparatus was used *without* anesthesia, up to 300 mm. Hg pressure. The intrauterine bag has obvious disadvantages, and it was not used lately.

These methods of investigation yielded peculiarly uniform results, and while typical uterine pain is accurately referred to the immediate suprapubic area in the midline of the lower abdomen, it sometimes reached as high as the umbilicus. This was true in 49 per cent of the patients examined. In 11 per cent of somewhat exceptional instances of primary uterine dysmenorrhea the passing of the uterine sound produced typical referred pain in some other

A SURVEY OF 113 CASES OF PRIMARY DYSMENORRHEA TREATED BY NEURECTOMY*

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BEFORE reading the technical part of this communication it is right and proper that I should show full appreciation for your invitation to deliver this Joseph Price Oration. Surely it is unnecessary to labor the fact that such an invitation, which is one of the highest honors that lies within your power to confer upon a colleague, not only does honor to me, personally, but also to Trinity College, Dublin, to the Rotunda Hospital, Dublin, and to the Dublin School of Medicine. I fully appreciate the high opinion you, in this great Country, hold of Irish obstetrics, and especially of that pioneer maternity hospital of which I am proud to say I am the present Master.

Although now chiefly concerned with obstetrics, I have been keenly interested for many years in the problem of dysmenorrhea and, without wishing to advertise the fact that I have written and worked considerably upon this subject, I cannot avoid referring occasionally throughout the text to my own publications.

I flatter myself that some points I have noted are advances in our knowledge, and it is for this reason that I put some facts and figures before you. I do not flatly contradict time-honored concepts, but I am convinced that many cases of primary dysmenorrhea are wrongly treated because of faulty diagnosis. Nor do I pretend to be able to explain with certainty why dysmenorrhea occurs—in other words, I am at a loss as to its exact etiology—but I am sure that in primary dysmenorrhea there are definite nerve lesions in the presacral, the ovarian, or both systems, and that menstrual pain usually can be relieved by appropriate and thorough nerve division.

I hope to be able to convince you that it is possible to differentiate between menstrual pain of ovarian or uterine origin, and also to show that dysmenorrhea may be a mixture of both. I also hope to clarify and dispel some doubts which exist regarding the harmful effects of nerve section upon the female genital organs, their fertility, and their reproductive powers. The cases under review were operated upon sufficiently long ago to enable me to assess the results confidently, and it is my belief that neither ovarian nor uterine denervation, nor combined ovarian and uterine denervation, assert a harmful effect upon a woman's vital functions. What follows has been most

*The Joseph Price Oration for 1948, delivered at the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 9 to 11, 1948.

gan, as found typically in *secondary* dysmenorrhea. My remarks will be thus confined to the cases which must be regarded as true *primary* ovarian dysmenorrhea. These constitute a certain proportion of our difficult cases; the grossly diseased ovary is readily recognized and accepted as a source of pain, but such pathology is unusual in the young patient in whom the typical symptoms of primary dysmenorrhea exist.

Sclerocystic changes in the ovary are of the greatest importance in ovarian dysmenorrhea, and were present in all my own cases, but some writers maintain that the small cirrhotic ovary with its thickened white capsule is an equally important etiological factor. L'Hermitte, and others of the French School, support the neurogenic etiological theory, and believe that ovarian sclerocystic changes are secondary to the influence of some ovarian nerve lesion rather than a primary condition. They regard cyst resection, or any other operation productive of ovarian scarring, as ill-advised and favoring recurrence of the symptoms by producing further cicatrization with fibrosis and pressure on the nerve endings. To support this there is very definite evidence of a peri- and intrafascicular ovarian nerve degeneration in such cases; some regard this as constant findings in ovarian sclerocystic disease, and similar degenerations are frequently found in about 70 per cent of the presacral nerves in intractable uterine dysmenorrhea.

I can confirm these findings relative to the presacral and ovarian nerve lesions in such cases, and it is interesting that none of these changes were found in the ovarian nerves examined from women who had not suffered from dysmenorrhea (i.e., the "controls") and for whom hysterectomy was performed for some uterine disease. Further "controls" within the dysmenorrhea age were also obtained when it was established that ovarian denervation did no harm to function.

If we accept the neurogenic theory of sclerocystic ovarian degeneration, and the association of pain with coincident ovarian nerve lesions, we can readily understand that only certain ovaries will be painful, and why it is that pain is an unusual symptom in the many and various sized ovarian cysts encountered. It also becomes apparent how "Mittelschmerz" may be totally absent in most women, but present or excessive in the minority whose ovarian nerves are abnormal. The two determining factors productive of excessive ovarian pain appear to be an existing nerve degeneration with pressure upon either the ovarian intrinsic nerves or some fibrils adjacent to the granulosa cell layer of a follicle. Such pressure could be continuous (from excessive fibrosis in the proximity of nerve endings) or periodic (from the edema present at the time of ovulation and in the premenstrual phase).

The question of pressure upon the fibrous or inflammatory nodules described by Neuman, and such nodules are now known to exist on the ovarian terminal nerve filaments in close relation to the ripening Graafian follicles, is particularly interesting. These nodules are most numerous in the prepubertal and postmenopausal ovary, being almost entirely absent around the follicles of the actively menstruating and multiparous woman. Their exact significance is unknown, but their frequent presence in those patients who are most liable to suffer from severe dysmenorrhea lends support to the neurogenic etiological theory.

The accepted ovarian lesions of *secondary* ovarian dysmenorrhea, e.g., a prolapsed and grossly cystic ovary, a small ovarian endometrioma or abscess, oophoritis, ovarian apoplexy, light pelvic adhesions, ovarian varicocele, parovarian tumors, are outside our present consideration. Celibacy, masturbation, or too frequent coitus, were believed by Ashton to cause ovarian con-

lower abdominal area. In most of these girls there was some palpable pelvic abnormality (*secondary* dysmenorrhea); the consideration of these is outside the scope of this paper, but undoubtedly the associated pathological conditions are responsible for the abnormal pain distribution.

The passing of the sound was absolutely painless in approximately 36 per cent of patients, many of whom did not suffer from dysmenorrhea; it produced pain referred exactly to the umbilicus in 2 per cent, and to the midline of the vulva about the position of the clitoris in the other 2 per cent. From these data we can separate with some accuracy the cases of true uterine pain from those of ovarian origin, and likewise interpret correctly co-existent mixed ovarian and uterine symptoms.

True primary ovarian pain is referred with equal frequency to either side of the lower abdomen, but diffuse lower abdominal pain probably indicates mixed dysmenorrhea of both uterine and ovarian origin. Ovarian pain itself appears typically in the two or three premenstrual days, rarely persists after the onset of the flow, and sometimes disappears before bleeding begins. In contrast, although uterine pain may be occasionally premenstrual in onset, it usually begins with the flow, ceasing after an hour or two, or persisting until the bleeding has completely ended. Ovarian pain is nauseating in character, being of a continuous dull, dragging type, and is probably similar to that evoked in the male as a result of trauma to the testis. Ovarian pain can be faithfully reproduced by evoking the "deep sensibility reflex" of the ovary by pressure upon one or both ovaries during bimanual examination, and radiation down the thighs (the viscerosensory reflex) often can be produced in this way. Only occasionally is uterine pain evident as a dull ache; in dysmenorrhea it varies typically in intensity being subject to exacerbations and is frequently sharp, stabbing, cramplike or colicky in character.

In brief, ovarian pain may be uni- or bilateral; menstrual but chiefly premenstrual; always subumbilical, but chiefly left-sided and radiating down the thighs. Although not included above, nausea is an almost constant symptom, whilst dyspareunia, dyschezia, and syncope are frequently present.

It should be comparatively easy, therefore, to separate the various types of primary dysmenorrhea from one another and to apply more specific treatment for their relief. Hormonal treatment, cervical dilatation, uterine curettage, and all other measures directed toward the relief of supposed uterine spasm, should be reserved for appropriate cases.

It may have no bearing upon the etiology or treatment of primary dysmenorrhea but the following interesting facts emerge from analysis of Tables I, II, and III.*

	ONSET OF PAIN	AGE AT OPERATION
Primary uterine dysmenorrhea	20.8 years	24.2 years
Primary ovarian dysmenorrhea	18.5 years	23.7 years
Primary combined dysmenorrhea	19.7 years	23.2 years

From this, it seems that most cases of intolerable menstrual pain reach a climax between 23 and 24 years of age, but that pain of primary ovarian origin has an earlier onset than that of primary uterine pain. It is only to be expected that menstrual pain of mixed origin would manifest itself midway between both varieties.

Lesions and Abnormalities of the Painful Ovary.—For the purpose of this discussion I will consider the painful or tender (though apparently normal) ovary, and exclude the frankly diseased, adherent, inflamed, or enlarged or-

*Tables not published.

Their most recent technique was, in brief, the division of the two or three main ovarian nerve bundles in the mesovarium without interference with the ovarian blood vessels.

Independently, and without knowledge of their work, I carried out the same operation by a simplified technique on several patients, with most encouraging results. The failures were due to my then inability to separate the uterine from the ovarian cases, for what I describe as distinctive signs and symptoms of ovarian, uterine, and mixed dysmenorrhea followed later.

My technique for ovarian denervation still consists of simple division of both infundibulopelvic ligaments, their nerves and blood vessels, and simple ligation of the stumps with catgut. To avoid the possibility of elongation of the divided ligament with subsequent prolapse of the ovaries, the cut ends are sutured carefully to one another and, where necessary, ovarian and uterine suspension has been performed. Appendicectomy, when indicated, has been a routine procedure. My bilateral denervations have been most encouraging—the earlier cases of unilateral division were disappointing. This has already been referred to, and is probably due to the close crosslinkage nerve supply of the ovaries.

Ovarian Denervation

The twenty-one cases of primary dysmenorrhea treated by ovarian denervation alone (i.e., cases diagnosed as purely primary ovarian dysmenorrhea) gave the following results over the period mentioned:

3 failures	14.2 per cent
1 partial success	4.7 per cent
17 successes	80.9 per cent

Presacral Sympathectomy

Thirty-four cases of severe primary dysmenorrhea were regarded as being of essentially uterine origin and were treated by presacral sympathectomy. In some additional operative procedures were used, as appeared appropriate. The results of the presacral sympathectomy operations in these 34 cases were as follows:

4 failures	11.7 per cent
5 partial successes	14.7 per cent
25 successes	73.5 per cent

The Presacral Nerve.—The so-called presacral nerve is singularly accessible to the operator in its retroperitoneal position in front of the last two lumbar vertebrae within the space bounded laterally by the two common iliac arteries. The presacral nerve is usually a well-defined fine plexus (the superior hypogastric plexus) rather than a single, large trunk, and in only 3 per cent was its free exposure made difficult by the proximity of the pelvic mesocolon.

The presacral nerve contains sympathetic and parasympathetic elements, and its continuation through the middle and inferior hypogastric plexuses on the front of the sacrum finally links it with the nervi erigentes. From this plexus thus formed the nerve filaments and ganglia are distributed to the uterus closely following the main arterial supply. Eventually the intrinsic uterine innervation ends subperitoneally and beneath its endometrial lining; there is no evidence of penetration of the uterine lining by nerves, nor are ganglia common in the uterine muscular tissue.

Operative Technique (Presacral Sympathectomy).—I have no special technique in performing presacral sympathectomy. This operation has been ade-

gestion and resulting pain. They are, admittedly, possible factors in the production of dysmenorrhea, especially when a nerve lesion is present, and are often noted in case histories of patients suffering from dysmenorrhea, but Ashton's view has not received much support.

The Ovarian Nerve Supply (Intrinsic and Extrinsic).—To agree that ovarian dysmenorrhea can exist, either as an entity or in conjunction with menstrual pain of uterine origin, implies acceptance of the view that the two structures possess their own independent and separate nerve supplies. This is now known to be true. Learmonth, Mitchell, and other histopathologists still doubt the possibility of a direct anatomical connection between the tubal and ovarian nerve supplies, but the absolute independence of the uterine and ovarian systems is generally accepted. *Ovarian innervation is bilateral, and pain originating in one ovary may be referred either to that side or to the opposite side, or to both the affected and the normal sides.* The clinical importance of this fact is readily appreciated.

The ovarian nerve supply is chiefly sympathetic, being derived from the renal, intermesenteric, and celiac plexuses. The ovarian nerves enter the hilum of the ovary in two or three main trunks, and then split up within the substance of the organ to accompany the arterial ramifications and end outside the theca externa of the follicle. Any statements that the terminal nerve fibers penetrate the membrane granulosa have been disproved, but they form an extremely dense network around the follicle and are intimately connected with it. It is just possible that a few fine, terminal twigs may leave the ovary between the layers of the mesosalpinx to end near the Fallopian tube and uterine cornu, but their final destination is unknown.

The vascular state of the ovary is controlled by the (dilator) impulses of the few parasympathetic fibers in antagonism to the richer sympathetic (vasoconstrictor) supply. In an organ subject to cyclic variations this is undoubtedly of importance in the control of the degree of congestion and the possible production of pain. Consider what the male would experience were the processes of ovulation to take place monthly in the testes.

With reference to the possibility of harm being done to the ovary by surgical denervation, it is well to remember that the stabilization of vascular tone within an organ thus suddenly deprived of its control is known to be rapid and without ill effect, even when the organ in question is functionally dependent upon its nerve control. The ovarian function and cycle are under *hormonal* control, and both are unimpaired by nerve section except that pain impulses cannot subsequently spread thence to the higher centers.

Pathways for painful ovarian stimuli exist in the ovarian nerves, as is known to be so in the presacral system in connection with the uterus, and the success of ovarian denervation depends upon this.

The Treatment of Ovarian Dysmenorrhea

In 1929 L'Hermite and Dupont and, independently, Leriche suggested that a painful ovary could be rendered insensitive by denervation. They knew that Cotte's operation was proving successful in carefully selected cases of presacral sympathectomy and believed that a similar ovarian denervation should give satisfactory results. The report of their early work proved interesting for they soon realized that, owing to the nerve cross link between the ovaries, successful denervation was necessarily bilateral. They also found that a uterine suspension operation improved the results when retroversion was present, as did appendicectomy when there was evidence of appendicitis.

sis enlarge and crowd the villi to such an extent that, with maternal intervillous circulation greatly reduced and fetal circulation absent, rapid necrosis results. Toxemia follows dissemination of the poisonous products through the maternal circulation.

As will be noted from Spanner's illustration of the placental circulation (Fig. 10), spasm, affecting the sphincters of a single collecting vein, would affect only the dependent unit of villi, resulting in an isolated, sharply demarcated, oval or round area, appearing very dark on account of the stagnated blood (Fig. 3).



Fig. 11.—Sphincter in placental vein. Low power magnification (Spanner).

If a succession of collecting veins or the main collecting vein, into which the others empty, is involved, there would result a confluent hemorrhagic infarction extending through a considerable area of the placenta (Figs. 2, 3). *The isolated and confluent forms of the infarction are explained by the anatomical arrangement of the collecting veins of the placenta and the appearance is hardly susceptible to any other interpretation.*

Since there is a consistent association of hemorrhagic infarction with acute fulminating as well as subacute toxemia of pregnancy, the arrangement of the collecting veins and the presence of sphincters take on a special significance pointing to the probable sequence of events leading to toxemia of pregnancy.

On this basis, it is also understandable how areas of slight darkening of the placenta might arise from partial or nearly complete closure of the sphincters just before labor, too recent to cause recognizable toxemia, but congesting the veins sufficiently to make an appearance suggestive of a very early acute hemorrhagic infarction. Immediate cutting of the cord at birth and draining away venous congestion might well prevent areas of this suggestive appearance but would not affect true hemorrhagic infarction in which thromboses had already occurred, immobilizing the blood. In the present series, eight placentas were doubtful and four mistakenly diagnosed as toxic through this appearance, or infarction was possibly in the making.

Definite acute hemorrhagic infarction and toxemia may occur after an interval of seven to ten days following the last prenatal visit and cause a patho-

quately described by others, and each operator develops his own particular system. I am satisfied, however, that incomplete presacral neurectomy and incorrect diagnosis are the commonest causes of failure. It is also important to remove at least one inch of the individual nerve fibers or of the plexus itself. If this is not done re-establishment of nerve continuity may lead to recurrence of the pain.

Combined Ovarian and Uterine Dysmenorrhea

From the 82 cases of severe dysmenorrhea treated by nerve resection, 27 appeared to be of mixed ovarian and uterine origin. In these cases presacral sympathectomy was combined with bilateral ovarian denervation with the following results:

1 failure	3.7 per cent
4 partial successes	14.8 per cent
22 successes	82.2 per cent

The Nerve Findings and Histopathological Studies

Analyzing the specimens which have been examined, 49 were from the hypogastric (presacral) nerves, and 27 from the nerves of the infundibulopelvic ligaments. A total of 76 microscopical sections were examined and, as there was no gross variation in the sections obtained from either group, the following description will suffice for both. Many more sections than the number quoted were examined, but my collaborator, Dr. David S. Torrens, Professor of Physiology, Trinity College, Dublin, was unable to devote the necessary time to detailed records of all the cases.

The fixative generally used was Heidenhain's mercuric chloride salt solution ("Susa"), and paraffin sections were made in all cases. Mallory's connective tissue stain was found to be the most useful, and this and polychrome methylene blue were employed as a routine. We (O'D. B. and D. S. T.) have studied:

1. The normal tissues.
2. The changes in the nerve trunks.
3. The changes in the small ganglia which are commonly found in the hypogastric nerves.

1. *The Normal Tissues.*—Specimens of the hypogastric (i.e., the so-called presacral nerves) usually contain numerous well-defined bundles of nerve fibers. Some of these included only ten or twenty fibers, while others are much larger. Both myelinated and nonmyelinated fibers are present. Most of the myelinated fibers are small, but there are also some large fibers. The nerves are embedded in fibrous tissue, which also contains numerous blood vessels and varying amounts of plain muscle. The tissue from the infundibulopelvic ligaments is similar, but nerve bundles are fewer and, as a rule, smaller. Groups of ganglion cells lie here and there among the fibers of the hypogastric nerves, but are seldom present in the ovarian nerves. The nerve fibers in the infundibulopelvic ligaments are chiefly postganglionic. Large cells of chromaffin type may sometimes be found among them; they resemble the chromaffin cells often found about the hilum of the ovary and should not be mistaken for ganglion cells. Lymphoid tissue is frequently present among the hypogastric nerves. The general structure of the ovarian and hypogastric nerves is similar to that of autonomic nerves in other parts of the body. There is the usual variable, but quite small, amount of fibrous tissue in the nerve trunks between the nerve fibers; this forms an endoneurium.

The ganglion cells in normal specimens have the usual appearances of healthy autonomic ganglion cells, varying in size and shape, and filled with well-defined Nissl granules. The capsule of "satellite" cells, described by Davis and others, is seldom recognizable and the arrangement is, perhaps, more characteristic of cerebrospinal than of autonomic ganglia. As the silver techniques were not used it was not possible to distinguish certain features mentioned by Davis, such as the various cell types of Cajal.

2. *Changes in the Nerve Trunks.*—In what we regard as abnormal specimens there is a marked increase in the amount of intraneural fibrous tissue. In the normal nerves, carefully stained by Mallory's method, the fine collagen fibrils of the endometrium can be clearly seen; in abnormal specimens the endoneurial tissue, besides being greatly increased in amount, often appears structureless and hyaline. In many specimens some of the nerves seem to be quite normal; in other nerves from the same specimen there is extensive involvement. The gross inflammatory changes described by Davis, such as infiltration of the nerves with polymorphonuclear cells, lymphocytes, and plasma cells, microscopic abscess formation, etc., have not yet been observed in our cases; nor have we found the advanced arteriosclerotic changes he describes.

Identical changes have been repeatedly observed in the ovarian and presacral nerves, and it is believed that a similar process may affect either, or both, systems. In addition to an intraneural fibrosis, a perineural fibrosis is present in a small proportion of cases; this, however, appears to be the exception rather than the rule.

3. *Changes in the Ganglia.*—These are commonly more marked than the changes in the nerve trunks. In abnormal specimens there is a definite increase in the number of small cells in the tissue between the ganglion cells. Whether this increased population is due to proliferation of local "satellite" and other cells, or to immigration of cells from other places (e.g., from the lymph nodes frequently present), or to both causes, is unknown. Some of the small cells may be lymphocytes or plasma cells, but many of them appear to resemble microglia or "Hortega cells." In addition to these small cells, large wandering cells resembling "mast cells" are frequently present in small numbers in the ganglia, but less frequently in the nerve trunks.

Many of the small cells under consideration are found clustered around and upon the bodies of the ganglion cells, and actual phagocytosis of the ganglion cells (neuronophagia) is common. The ganglion cells also show degenerative changes, pigmentation, chromatolysis, and disintegration, and here we are able to confirm the observations of Davis. We suggest that the ganglion cell may be the primary focus of an attack by the unknown causal agent, for in several specimens the ganglia are affected while the nerve trunks appear normal. Conversely, in specimens where the nerve trunks show definite fibrosis, the ganglia are always seriously involved, and many of the cells damaged and destroyed. The changes we have constantly observed may be summarized as:

1. Degeneration and destruction of sympathetic ganglion cells.
2. Degeneration of postganglionic fibers.
3. Replacement fibrosis in the nerves.

There are, clearly, two questions which require consideration:

1. What is the cause of the changes in the nerves?
2. What is the relation, if any, between the nerve changes and dysmenorrhea?

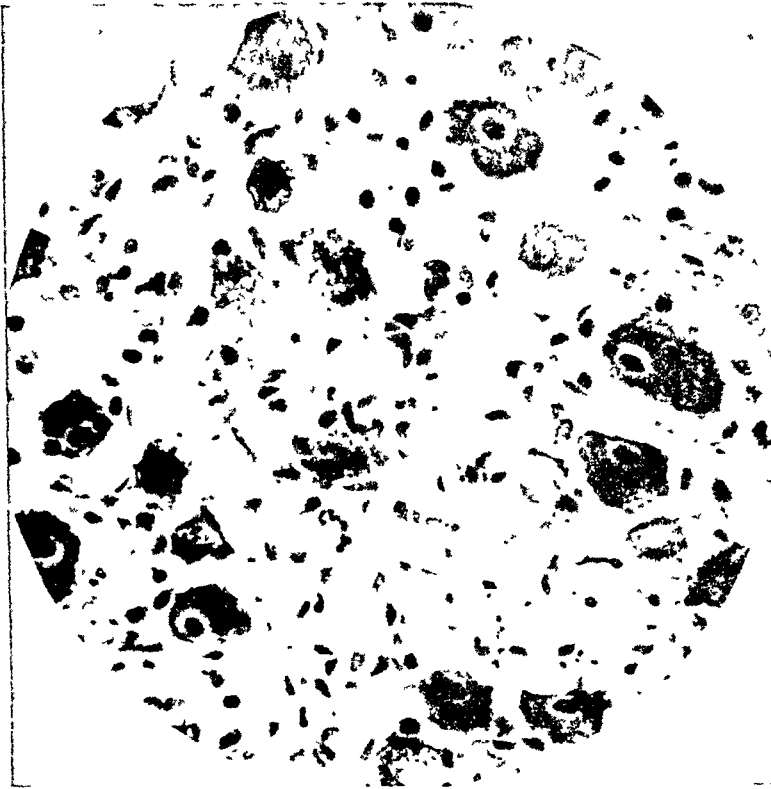


Fig. 1.—Ganglion cells from Case K. R. 9. Regarded as normal. Healthy cells with typical Nissl granules and with very few "satellites." No appearance of infiltration with other types of cell.

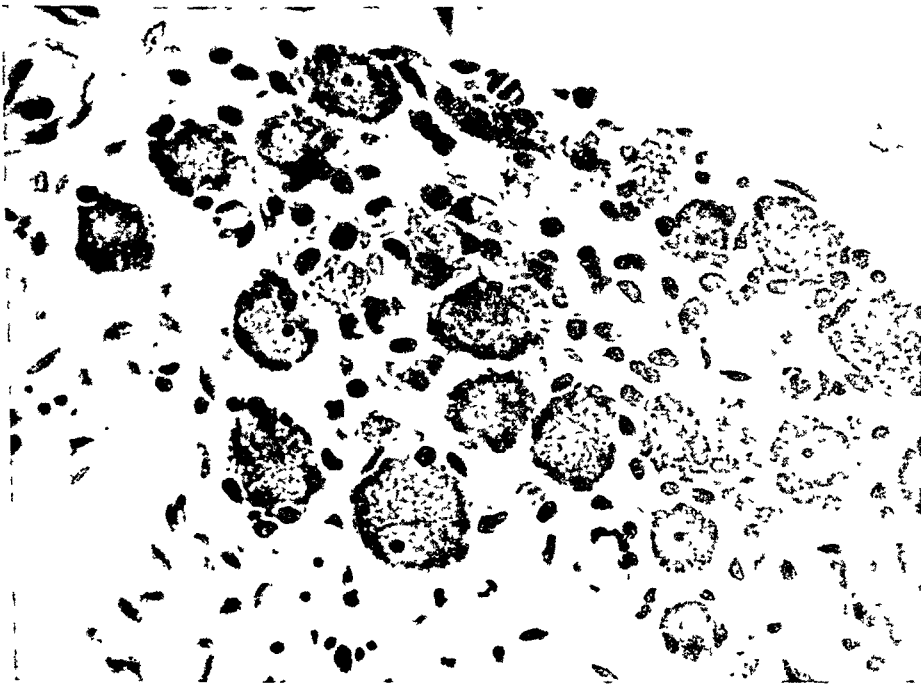


Fig. 2.—Ganglion cells from Case A. H. 1. Regarded as abnormal. The cells show some chromatinolysis, and there is a definite increase in the number of small cells possibly of microglial type. Many of these are concentrated about and upon the ganglion cells, and there are indications of some neuronophagia.

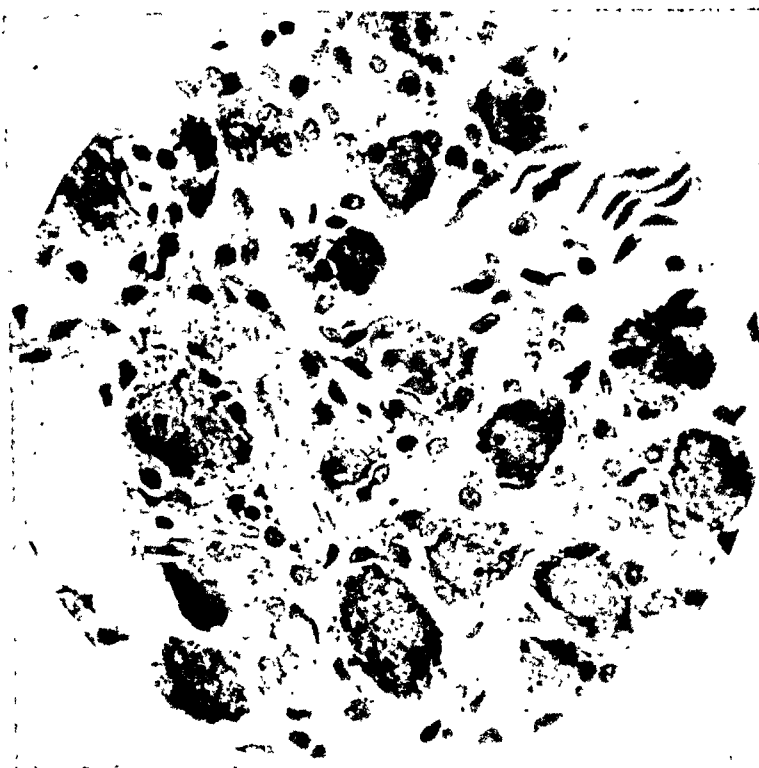


Fig. 3.—Ganglion cells from Case B. F. 11. Regarded as abnormal. The condition is very much the same as that seen in Fig. 2.

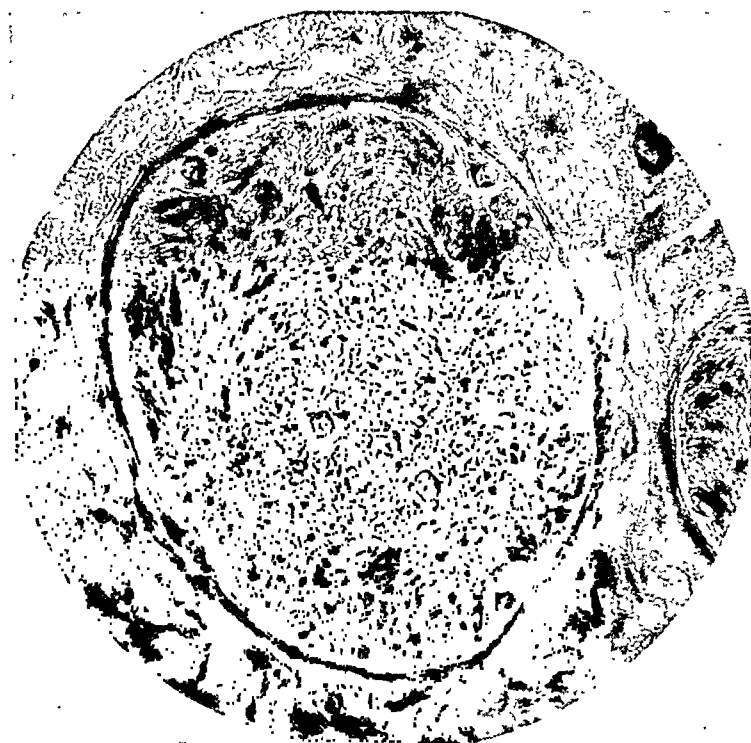


Fig. 4.—Nerve trunk (presacral) from Case K. R. 9. Regarded as normal. Shows myelinated and nonmyelinated fibers. Note relatively small amount of endoneurial fibrous tissue.

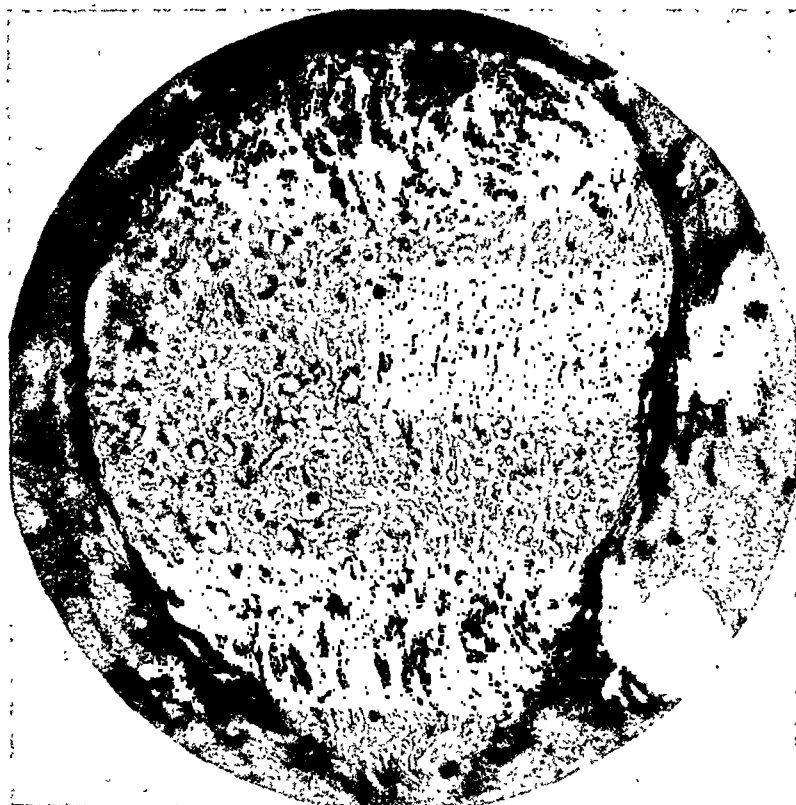


Fig. 5.—Nerve trunk (presacral) from Case B. H. 13. Regarded as abnormal. The endoneurial fibrous tissue is increased and many nerve fibers are almost obliterated.

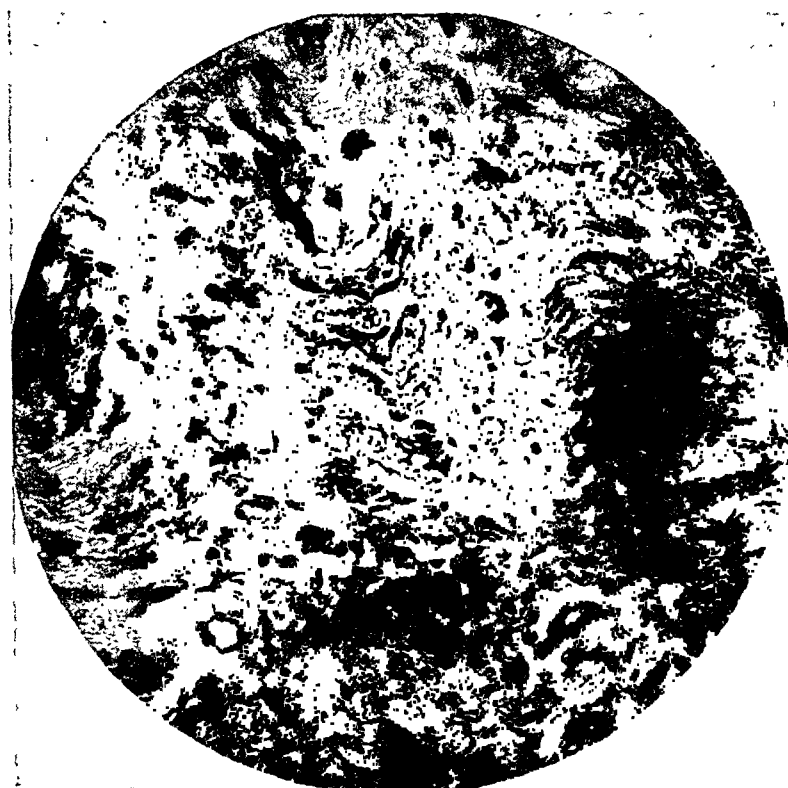


Fig. 6.—Nerve trunk (presacral) from Case B. F. 11. Regarded as abnormal. The endoneurial fibrous tissue is increased and shows what appears to be hyaline change.

Neither question can yet be answered with certainty. The appearances seen in the nerves of both systems are somewhat similar to those found in cerebrospinal nerves and the root ganglia in zoster and certain types of toxic neuritis, such as arsenical neuritis. Comparable changes are also found in the nerves in animals suffering from vitamin B₁ deficiency, and in human beings with beriberi.

The relation of the nerve changes to pelvic pain is also far from clear, but certain facts may be indicated. The hypogastric and ovarian nerves contain not only the sympathetic afferent supply to the pelvic viscera, but also sensory afferent fibers from these organs. We believe that the afferent nerves are first attacked, some of the ganglion cells becoming involved, and that their axons, the postganglionic fibers, consequently degenerate. It seems probable that the sensory fibers are secondarily implicated, possibly as a result of the fibrosis. The pain of dysmenorrhea clearly is not due to direct involvement of the sensory fibers, for if so it would be constant and continuous, and not specially related to the menstrual cycle.

It appears probable, therefore, that the sensibility of the fibers may be altered so that the sensory impulses from the uterus or ovary, which normally do not produce pain, become painful. It has been shown by others that attacks of severe menstrual pain generally coincide with the uterine movements. The uterine movements, normally painless, thus become painful if the sensory nerves are hypersensitive. In contrast, dysmenorrhea of ovarian origin is chiefly or exclusively premenstrual in occurrence, and coincides with the congestion and increased tension in the ovary at this phase.

A further possibility is that, in the early stages of attack and before the ganglion cells are destroyed, the causal agent may produce irritation and increased activity of the cells. This may lead to an increase of uterine motility, which would reach a climax during the menstrual period and cause visceral pain by the usual means. The vasomotor activity of the nerves may also be of importance. Vasomotor disturbances of the uterus may be a source of pain, but in primary ovarian dysmenorrhea the vasomotor condition is probably the chief factor since muscular action can play little or no part.

Fertility Subsequent to Any Form of Nerve Resection

In reviewing the 82 cases which replied to my 1945 questionnaire, thirty were either married before operation or married subsequently. Analysis of these potential mothers shows that:

Eighteen produced full-term living children, without undue trouble.

Two miscarried.

Two who had been married only a few months at the time they received my questionnaire could not be regarded as conclusive evidence in reviewing the results.

One unmarried girl had a normal pregnancy and delivery.

Thus, twenty out of a possible thirty married women showed a high rate of fertility, a percentage parturition rate of 66.6 per cent, which compares favorably with statistics from a cross section of the normal adult female population in my country. No effort was made in this series to correct the final fertility rates by detailed investigation of the husbands but, presumably, any lack of fertility would be subject to an average male infertility rate of 25 per cent. If we accept this it would be fair to add a further 25 per cent to the figure of 66.6 per cent. This leads us to believe that the operations of

presacral neurectomy and bilateral ovarian denervation do not endanger fertility.

The two patients too recently married to be included in this summary probably would have added support to this statement, and we can quote the one further case where an unmarried girl was delivered of a healthy child subsequent to operation.

My experience also shows that labor following any form of nerve resection was neither abnormal, nor easier, nor more difficult than the average. In no instance was there any evidence of either bladder or bowel disturbance.

The Association of Failure of Relief With the Nerve Findings of Microscopical Sections

There were three failures (14.2 per cent) and the twenty-one cases treated by bilateral ovarian denervation alone. Unfortunately, no nerve sections are available in these (some of the notes were mislaid), and no conclusions are possible from microscopical evidence. It is, however, interesting that in one case (No. A.D.) bilateral ovarian denervation failed, but complete relief subsequently followed a second operation, presacral sympathectomy. This further emphasizes that dysmenorrhea can be of either uterine, ovarian or mixed origin, and that usually a clear-cut diagnosis should be possible.

The details of the microscopical sections in the nerves in three of the four cases of failure by presacral sympathectomy alone can be seen in Table II. They are inconclusive, varying degrees of fibrosis being present. In one case (No. E. F.) the presacral neurectomy operation was difficult, and it is probable that the nerve resection was incomplete. The other three cases supply no useful information but, as has already been stressed, incomplete nerve resection and incorrect diagnosis are the probable causes of failure.

From Table III, case No. M. H. was the only failure in the 27 women for whom combined presacral neurectomy and bilateral ovarian denervation were performed. This illustrates that unless our diagnosis is precise it is better to use the combined operation of presacral sympathectomy and bilateral ovarian denervation than to rely solely upon one procedure.

On studying the nerve sections from this case we found there was extensive and advanced fibrosis both in the presacral nerves themselves and in their ganglia, and that the ovarian nerves on one side were also similarly affected. Despite the fact that the operation did not cure this woman's pain she subsequently became pregnant and produced a living child without difficulty. It is at present impossible to correlate nerve degeneration and operative treatments with fertility, but it seems established that nerve division does not impair reproductive function in the female.

Incidence of the Various Types of Dysmenorrhea

In the cases under review, as judged by the results over a period of years, primary ovarian dysmenorrhea existed as a clinical entity in 21 out of 82 cases, or 25.6 per cent. Primary uterine dysmenorrhea is more frequent (41.4 per cent), and the follow-up on the 27 cases for which both presacral and ovarian denervation were performed suggest that combined ovarian and uterine dysmenorrhea exists in 33 per cent.

When these figures are compared with my original conclusions, as published in 1939, we find that I then believed that ovarian dysmenorrhea alone existed in only 11.9 per cent of all cases of dysmenorrhea, but that it could be present in association with dysmenorrhea of uterine origin. My estimate was, therefore, too low since further time has shown the incidence to be 25.6 per

cent. I was also of the opinion that 25 to 30 per cent of cases of severe dysmenorrhea were of mixed uterine and ovarian origin. The present facts seem to indicate that this incidence of this type is 33 per cent, and that primary uterine dysmenorrhea completes the remaining 41.4 per cent. It must be stressed again that these figures are only relative to primary dysmenorrhea and do not include those in which gross pelvic pathology exists.

Objections to the Operation of Neurectomy

It is only natural that I should have been criticized from time to time for subjecting young women to what many, chiefly older gynecologists, consider an unjustifiable and unnecessary operation. Many routine operations we perform today would have been considered unnecessary some years ago, but the constantly increasing safety and the lessened discomfort to those upon whom we operate now make our work justifiable for conditions which are not necessarily fatal. A little thought on this subject makes the point quite clear, and I do not regard operative treatment to relieve menstrual pain unjustifiable when other less radical treatments have either failed or are unlikely to succeed. It has been my rule to try less radical treatments before resorting to laparotomy.

It is not uncommon to be asked, either in all seriousness or by way of banter, how many times I have cut or injured the ureter during presacral neurectomy. I am glad to say that this accident has not happened, and there have been no serious postoperative complications. On one occasion it was necessary to reopen the abdomen the evening of operation for postoperative bleeding, which occurred in one of my earliest cases of division of the infundibulopelvic ligaments. The ovarian pedicle is notorious for its tendency to retract when divided, and to shed (or "roll off") its suture. This had happened, but the nature of the complication was suspected and, at laparotomy, nothing more was necessary than to apply a fresh ligature. This was followed by an uncomplicated recovery.

It has already been mentioned in this text that the objections of possible interference with either a woman's fertility or sexual life as a result of nerve section are groundless. I wish to emphasize this, for I feel that I can speak with authority having carefully followed such cases for so many years.

To conclude my comments on the justifiability of abdominal operations for the treatment of dysmenorrhea, may I add that I think it wrong to withhold nerve section if it is likely to afford relief. There is no reason to fear a catastrophe, even if presacral neurectomy is combined with bilateral ovarian denervation. In my series there has been *no* fatality, and the operation is less likely to be followed by postoperative complications than is the simple appendicectomy.

How Does Nerve Section Relieve Pain?

This is a point about which there has been much discussion, but finality has not yet been reached. It seems logical to conclude that, if the nerves of the various plexuses contain afferent fibers, their division will block pain impulses passing to the higher centers. It follows, therefore, that incomplete nerve section will not relieve pain, and that pain will continue if an incorrect diagnosis has been made and the wrong nerve system divided.

It can be argued that primary uterine dysmenorrhea, as distinct from ovarian pain, may be due to ischemia of the uterine muscle, and that presacral neurectomy abolishes the vasoconstrictor influence. This is a further possible explanation, but it is not one which is generally accepted even if the

hypothesis is correct. The relief of pain thus afforded probably would be transient, for an organ deprived of its nerve blood vessel control stabilizes this of its own accord. Thus, recurrence of pain would be the rule rather than the exception.

Much has also been written about the possible effect of nerve control upon maturation of the follicles within the ovary but, on practical grounds, there is no support for the view that ovarian blood vessel balance is altered considerably following complete division of the nerve supply.

It may be concluded that, while we do not certainly know how pain is relieved following nerve section, the most likely explanation is the break in continuity of afferent nerve fibers.

Etiology of Dysmenorrhea

While it is quite impossible to devote time to discuss even current theories on the etiology of primary dysmenorrhea, several may be discarded without apology. I again emphasize the confusion existing between primary and secondary dysmenorrhea, and the scant attention devoted to their differential diagnosis.

I am quite satisfied that the old theory of obstruction to menstrual debris, either at the internal os or in the cervical canal, is incorrect. In my experience cervical stenosis is rare, and the truth or otherwise of this statement can be readily proved.

It may be asked why cervical dilatation relieves pain, even without curetting. I am unable to answer this any better than can our textbooks, but it is a pity these authorities do not stress the fact that the relief of primary dysmenorrhea following cervical dilatation rarely lasts longer than six months. When the pain returns there is recourse to a further dilatation, a nerve section, or some other treatment. Too often do we too lightly perform cervical dilatation, hoping for the best while shutting our eyes to the fact that its benefits are but short lived.

It must be remembered that the remarks throughout this text on the diagnosis and treatment of dysmenorrhea are confined to the complaint in its primary form. I have found no form of nerve division helpful when coincident pelvic lesions have been present. A high percentage of my failures have been due to nonrecognition of this, and I stress this fact so that those who may be tempted to test the efficacy of nerve section to relieve dysmenorrhea in general will refrain from doing so should any gross pelvic pathology be present.

You may be sure that I have given very careful thought to this problem, and state confidently that I regard our present classifications of dysmenorrhea as misleading. They are satisfactory for examinations, but get us no nearer to what matters, namely, the certain relief of menstrual pain.

Having spoken so dogmatically about dysmenorrhea it is to be expected that some of you may say, "Well since you pretend to know so much about it, what causes primary dysmenorrhea?" I must answer truthfully, "I do not know," but that does not prevent my having ideas on the subject. Since dysmenorrhea is more prevalent and intense in what we call the more civilized peoples and in the higher social groups than in the lower brackets, it is my belief that our so-called civilization is the root of the evil, and that if our young women led more normal lives fewer would suffer menstrual discomfort. Our religions, our education and upbringing, and convention honored throughout the world for many years have dictated celibacy before marriage—and here civilization is in direct conflict with Nature. It cannot have

been thoughts upon this subject that prompted the great Samuel Johnson to write, "Marriage has many pains, but celibacy has no pleasures," but his words cannot be considered altogether inappropriate. It is undoubtedly a misquotation here, but your own Oliver Wendell Holmes wrote in "The Poet at the Breakfast Table,"

"When she was a girl (forty summers ago)
Aunt Tabitha tells me they never did so."

Times have not changed markedly, women probably not at all; dysmenorrhea persists.

While I disagree with the old teaching that a woman who has a baby subsequently enjoys almost complete relief from menstrual pain, I am convinced that were cases of severe dysmenorrhea following parturition thoroughly investigated they would be found to be of *secondary* rather than *primary* nature. To put the matter concisely—I believe that so long as our present moral code is observed and young women are denied the dictates of nature, so long will dysmenorrhea continue to be a scourge. But from this do not infer that I am asking you to advocate free love; that *might* be an answer, but I do not recommend putting it to the test!

Possibly some of my audience will say, "Many girls have a moral code which fits your theory, yet they suffer dysmenorrhea." I agree; in many instances this is correct, but again I ask you how many of these cases have been intelligently investigated and proved to be examples of *primary* dysmenorrhea? Only too often do these girls develop pelvic lesions from gonorrhea and other infections.

You may ask, "Supposing your theory is correct, and the leading of life in accordance with the individual dictates and urges relieves the pain of primary dysmenorrhea, how does this happen?" Again, I cannot answer you, but nobody can deny that repressions, the absence of repeated pelvic hyperemia such as accompanies satisfactory sexual intercourse, and the dissatisfactions which follow the abstinences enforced on the many by the trend of life and moral code play their parts. In the absence of gross pelvic pathology the occasional pelvic hyperemia of menstrual periods quite understandably produces pain. Were the pelvic organs and their blood and nerve supplies exercised earlier, and more regularly, by free sexual intercourse (and possibly pregnancy) this severe monthly menstrual engorgement pain would fade into insignificance.

We know little, too, about what effect the enormous blood hormone levels associated with pregnancy have upon a woman's genital apparatus. We attribute the softening of the pelvic structures, even that occurring in the ligaments binding the bony pelvis together, to hyperemia. But is this enormous change entirely the result of hyperemia? Surely the hyperemia of pregnancy and the changes in the ligaments, the pelvic fascia, and the uterine supports throughout the genital tract must be largely due to hormone effect.

In concluding these speculations it seems as if we may compare primary dysmenorrhea to a deficiency disease. It may be asked then, "Why is hormonal therapy so disappointing in these cases?" The answer is probably that we little appreciate the enormous dosage required and our estimates are too low.

Before ending I wish to thank Professor David Torrens and his staff, and all my colleagues at Sir Patrick Dun's Hospital, for their encouragement and help. I am especially indebted to my secretary, Miss May Walmsley, for unfailing and helpful enthusiasm in the tiresome collection of these data.

logically positive placenta to be associated with an apparently clinically negative patient. This accounts for an occasional discrepancy in the clinical and pathologic diagnoses on examining "unknown" placentas.

From the foregoing clinical and pathological evidences, it would seem logical to put abruptio placentae in its rightful place as a manifestation of toxemia. Without minimizing the danger from excessive loss of blood in this condition, the associated toxemia has a greater bearing on the mortality and the rationale of treatment than the hemorrhage. One can successfully cope with the loss of blood, but the basic toxemia, with tendency to shock, lessens the patient's ability to withstand trauma and surgical measures.

The time-honored association of placenta previa and abruptio placentae in the textbooks, with the main consideration given to the hemorrhagic aspect of the problems and to surgical treatment, is eminently correct regarding placenta previa but tends to place undue emphasis on surgical interference in abruptio.

It seems more a matter of expediency to recommend cesarean section for severe cases of abruptio placentae found to show little or no dilatation of the cervix at first examination, when it must be admitted, if the same case had been seen for the first time several hours later, the cervix would have shown considerable dilatation and natural delivery would therefore have been recommended (Cases 2, 4, 7, 11, 12, 45, 46, 49).

Miller,¹⁰ by plentiful use of transfusion, was able to show excellent results by cesarean section, but there is reason to believe the same cases would have done equally well with the same blood replacement and natural delivery and future childbearing would not be complicated by a uterine scar. Many cases in our series illustrate this contention.

If there is present that grave but rare disturbance in the blood-coagulating mechanism occasionally found in abruptio placentae, with tendency to uncontrollable bleeding into the tissues as well as from the uterus, it apparently makes very little difference in mortality whether the patient is treated conservatively or by cesarean hysterectomy.³ Hope for these patients must rest on means of early detection of hemorrhagic tendency. It is admitted in these cases, if serious hemorrhagic tendency can be detected, cesarean section, if resorted to early, may be a lifesaving measure by promptly removing the placental source of the toxin.

If we regard hemorrhagic infarction of the placenta as the source of the toxemia, it does not seem logical merely to control eclamptic convulsions and procrastinate thereafter in terminating the pregnancy. To delay is to permit further damage to vital organs and risk further convulsions through new infarctions.

When abruptio and complete separation of the placenta take place, as evidenced by fetal death, no further absorption of toxins can take place at the placental site. Hence, the mere presence of the fetus and placenta in the uterus should not influence the prognosis. With tendency to limitation of further blood loss by intrauterine pressure, aided if necessary by small and carefully controlled doses of Pitocin to hasten labor, if artificial rupture of the membranes is not quickly effective, and lessening shock and anemia by repeated blood transfusions, we may encourage and await natural delivery.

Simple Classification of True Toxemia of Pregnancy

Finally, it would seem logical to simplify the present classification of the toxemias of pregnancy. One may sense in the opinions expressed in the literature that renal and vascular disease have nothing in common with true toxemia of pregnancy except the associated hypertension. The fact is recognized,

Nomenclature

Pelvic inflammatory disease is a dynamic process and the terms acute, chronic, subsiding, spreading, recurrent, and quiescent are all descriptive of some phase of the process which usually can be recognized clinically. The term chronic is not descriptive of the process which follows acute attacks of pelvic inflammatory disease and should be used only when it refers to reactions such as those caused by tuberculosis, foreign bodies, and other agents which induce slowly progressing processes.

Causes of Pelvic Inflammatory Disease

The irritants which cause pelvic inflammatory disease are many, but may be classified I think into two groups, namely, those of *bacterial origin* and those caused by some physical force or change in the status of the structures in the pelvis.

The inflammatory processes of bacterial origin are thought to be caused most often by the gonococcus, the streptococcus, the staphylococcus, the colon bacillus, the welchii bacillus, pneumococcus, tubercle bacillus, and the mycoses, which are recognized causes. There undoubtedly are others which have been unrecognized. The physical changes in the pelvic viscera which may cause pelvic inflammation are almost unlimited, and I shall enumerate some of the usual ones, viz., ruptured Graafian follicle, endometriosis, twisted ovarian cysts, twisted pedunculated pelvic tumors, degenerating myomas, tubal abortions and ruptured ectopic pregnancies, hemorrhage into pelvic tumors, torsions of the pelvic viscera (uterus, tubes, and ovaries with the torsion of the uterus with the cervix as the axis), ruptured endometrial cysts, diverticulosis of the sigmoid and many others. All of the above conditions have been observed by me, and it is my impression that the reaction induced by these changes is an inflammatory one, and one is justified in classifying all of them as pelvic inflammatory disease with the cause stated as it can be determined. In many instances, the cause cannot be determined definitely and sometimes not at all because the patient has recovered spontaneously from the process which has made further study or observation unnecessary or prohibitive.

The three most common types of pelvic inflammation of infectious or bacterial origin are stated as the gonorrheal, the septic, and the tuberculous. These three types of infectious or bacterial pelvic inflammation have been recognized clinically for a long time.

Pelvic inflammatory processes of infectious or bacterial origin generally can be considered to have characteristic methods of behavior and I think they arise from a focus that communicates with or is contiguous to the internal genitals.

Pelvic inflammatory disease of infectious or bacterial origin seems to extend either by surface extension or interstitial extension.

1. Pelvic Inflammation by Surface Extension

It would seem that this type of pelvic inflammation has its origin from a focus of infection in the lower genital tract, that is, an endocervicitis, a urethritis, or a Bartholinitis. I think it is usually transmitted to the upper genital tract by some physical force which mobilizes the organisms from the lower to the upper genital tract. The type of physical force may be coitus, traumatic treatment, high-pressure douches, and activities which would increase intravaginal pressure. As the organisms migrate from their original

A STUDY AND CLASSIFICATION OF PELVIC INFLAMMATORY DISEASE*

ROY W. MOHLER, M.D., Sc.D., PHILADELPHIA, PA.

THIS presentation is being made because of my interest in pelvic inflammatory disease and because much that has been written and is being taught about it does not correspond to accepted concepts of the behavior of inflammatory processes in other body structures. Because of these two premises, I believe it might be worth while to present some thoughts which seem to me pertinent. I hope this presentation will promote some discussion and increase our interest in this important subject.

Definition

Pelvic inflammatory disease can be described as a tissue reaction to some irritant which involves the internal female genitals and their contiguous structures. This reaction causes certain signs and symptoms which may be recognized clinically. The structures involved would ordinarily include the uterus and its adnexa, the parametria in its broadest sense, and the pelvic peritoneum, and sometimes the rectum, sigmoid, and cecum. This definition is basic and corresponds to the accepted concepts of inflammation and its cause in all body structures.

To understand clearly why pelvic inflammatory disease behaves as it does, we must appreciate the two characteristics of the female genital tract which are anatomical and physiological. The anatomical characteristic is the fact that the female genital tract during the procreative period of the individual is patulous and there is normally a communication between the external environment of the individual and the peritoneal cavity, and its fundamental physiological characteristic is its adaptability to procreation. If we consider pelvic inflammatory disease with these fundamental facts as basic, it could be much easier taught to students, and it seems to me that our concepts correlate much better with generally accepted ideas of inflammation in other body structures.

Symptoms and Signs

The main symptom of pelvic inflammatory disease is generalized pain of varying intensity limited to the lower abdomen. The signs of the condition are temperature elevation of various degrees, rigidity, tenderness and muscle guarding of the lower abdomen, and pain and tenderness of the internal genitals when an effort is made to outline them through the vagina. The blood count shows various changes which demonstrate its reaction to inflammation. The erythrocytic sedimentation time is reduced. Symptoms and signs indicate that the internal genitals and a localized area of the pelvic peritoneum and its contiguous structures are reacting to some irritant by an inflammatory process.

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structures become involved in this process, it is the interstitial or surrounding areas which are affected and not the mucosal surfaces.

Tuberculous pelvic inflammation is relatively infrequent and can be referred to as a chronic inflammatory process. It can be thought of as developing from a focus of tuberculosis elsewhere in the body and is probably of metastatic origin. From a pathological standpoint it may be a surface process or an interstitial one and its powers for destruction are very extensive.

Pelvic Inflammation Caused by Changes in the Status of the Genitals

Pelvic inflammatory disease caused by physiological changes in the internal genitals and pre-existing tumors of these structures is a very definite entity and because the patient recovers spontaneously from the process, it is often assumed that a pelvic inflammatory disease of infectious origin has been present. It is my thought that many of these processes are definitely inflammatory processes of noninfectious origin and are serious enough to warrant definite recognition and sometimes prompt surgical treatment.

I shall cite two clinical examples of what I have in mind with the histories of two patients admitted recently to Jefferson Hospital in Philadelphia:

CASE 1.—Mrs. M. W. (6216), aged 36 years, Negro, gravida iv, para iv, was admitted to the Gynecological Ward of the Jefferson Hospital on Oct. 14, 1947, with a complaint of irregular menstrual periods and feeling of fullness in the pelvis. After the birth of her last child in 1937 her periods recurred only once a year. In 1944 she had an attack of "peritonitis" requiring hospitalization elsewhere. When first seen at Jefferson Hospital Outpatient Department on Oct. 9, 1946, a tentative diagnosis of pelvic inflammatory disease and myoma uteri was made. On admission to the Jefferson Hospital Ward on Oct. 14, 1947, she had vaginal bleeding which had been present for three weeks. Pelvic examination revealed the uterus to be normal in size with a tender mass the size of a baseball attached to the right cornu. A preliminary diagnosis of myoma uteri was made. Following examinations the patient developed an elevation of temperature and leucocytosis. These changes were interpreted as indicating a flare-up of a residual pelvic inflammatory disease. On Oct. 17, 1947, the patient showed signs of internal hemorrhage and was operated upon. The abdominal cavity was filled with blood. A solid right ovarian tumor about 7 cm. in diameter was found to be ruptured and bleeding actively from several areas.

Pathological report showed the ovarian tumor to be a granulosa cell tumor.

Our clinical diagnosis before operation and our clinical findings on this patient were those of pelvic inflammatory disease. Observations and studies before operation and the changes in the pelvis at operation indicated a pelvic inflammatory process and it would seem that the accident which occurred to this pre-existing tumor was definitely responsible for the inflammatory process.

CASE 2.—Mrs. B. O., aged 44 years, was admitted to Jefferson Hospital on Jan. 17, 1947, with a chief complaint of abdominal pain of three days' duration. The patient had been well until the third day of her menstrual period, Jan. 14, 1947, when she experienced a continuous pressure-like pain throughout her abdomen. The pain increased in severity the next two days and was associated with an elevation of temperature of 100° F., mild chills, general malaise, and headache. Her family doctor prescribed oral penicillin which was taken for eighteen hours before admission to the hospital. On admission to the hospital the patient had generalized lower abdominal tenderness. On pelvic examination it was found that the uterus was incorporated in or attached to a pelvic mass which filled the pelvis and extended to the level of the umbilicus. The mass was soft but not definitely cystic. The impressions were an ovarian tumor or soft fibromyoma of the uterus. The patient was operated upon on Jan. 25, 1947. A large multilocular, cystadenocarcinoma of the left ovary the size of a five

focus, they extend along the mucosal surfaces of the various pelvic structures and then various local surfaces become involved in an inflammatory process and consequently an endometritis, endosalpingitis, and finally a pelvic peritonitis develops. Perioophoritis and a perisalpingitis usually follow the peritonitis. These processes are rather definite and understandable but since most of our conclusions must be based on observations made when operation was the treatment for them, these statements may seem arbitrary.

These processes appear to run a fairly definite cycle. There is severe pain in the lower abdomen, muscle rigidity, a high temperature reaction, a leucocytosis, and rather definite pelvic findings when the patient is examined vaginally. The clinical reaction to this process lasts about 72 hours, the temperature then subsides, and the physical condition of the patient improves. So far as we can tell clinically and in the few instances where observations have been made at surgical operation, the patient recovers completely, and it would seem that recovery has occurred spontaneously in spite of the fact that the sulfonamides, penicillin, and other antibiotics have been used in the last few years. The reaction of these patients would indicate that the inflammation of the internal pelvis has been a self-limited process, and that spontaneous and almost complete resolution of the process has occurred.

Why do these attacks of pelvic inflammatory disease tend to recur? 'It would seem that a reinfection develops because of a latent infection in the lower genital tract and it can be assumed that with each reinfection some slight residuum or change occurs in the pelvic structure, and with a number of reinfections, large pelvic abscesses and extensive adhesions, cystic changes in the ovaries, pyosalpinges, and adherent oviducts develop. These extensive changes are most often seen among Negro patients and are less frequently observed with white patients.

This characteristic reaction has been attributed to the gonococcus and until we began using cultures for the identification of the gonococcus, we were satisfied with our conclusions but in the light of present studies for the identification of the cause for these infections, it is my impression that the problem is not so simple and that we shall find other organisms than the gonococcus sometimes responsible for these surface-spreading infections.

2. Pelvic Inflammation by Interstitial Extension

This type of pelvic inflammation is most frequently caused by the pyogenic organisms and should be referred to as being of septic origin. The organisms are most frequently the streptococcus and the staphylococcus but other organisms may be responsible. These inflammations result from an inoculation of the organism into a break in the continuity of the protective surface of the genital tract and may, therefore, follow any trauma which has disrupted the genital surface, namely, diagnostic procedures such as dilatation of the cervix and curettage of the uterus, cauterization of the cervix, induced abortion, spontaneous interruption of pregnancy and certain other traumatic phenomena. Septic infections, however, are most frequently associated with the interruption of pregnancy, and, therefore, are often referred to as puerperal infections. These infections are interstitial in their progress and pass by way of the lymphatics and the cellular tissue of the pelvis. The involvement of the pelvic structures per se is secondary to the interstitial process.

These interstitial processes are frequently self-limited and the involvement is very slight. Abscess formation, however, sometimes develops. In a few instances, the process extends either into the blood stream or the peritoneal cavity and a septicemia or spreading peritonitis develops. If the pelvic

Discussion

DR. J. MASON HUNDLEY, Baltimore, Md.—At the University of Maryland we strongly emphasize the conservative treatment of tubal disease, especially that due to the gonococcus and with the advent of chemotherapy the incidence of necessary operative procedures has greatly decreased, approximately only 15 per cent of the patients coming to surgery. With us the indications for operation are as follows: 1. painful, fixed retrodisplacement; 2. adhesions with symptoms; 3. metrorrhagia and menorrhagia associated with marked dysmenorrhea; 4. large hydrosalpinges or tubovarian abscesses; 5. repeated attacks of infection.

Conservation of tissue is stressed, especially in the gonococcal group. However, with advanced pathology due to the streptococcus or tubercle bacillus, the procedures are of necessity more radical for here the organisms are long lived and virulent which is in contrast to the gonococcus.

An interesting historical digression is in regard to the specificity of the gonococcus and is of especial interest to the physicians of Baltimore, for it was here that Phillipe Ricord, between 1830 and 1840, did his monumental work inoculating hundreds of men with gonorrheal pus and in none was he able to produce syphilis. Even at this late date, due to the teachings of Sir John Hunter, it was believed that gonorrhea and syphilis were the same disease in spite of Sir John's developing syphilis after inoculating himself with secretions supposedly from a case of gonorrhea.

The study of tuberculous salpingitis is of interest primarily due to its apparent infrequency. In a survey of 1,092 patients with salpingitis there were only 22 due to the tubercle bacillus, an incidence of 0.2 per cent. The majority of textbooks state the occurrence of tuberculous salpingitis in the order of 5.7 per cent; this decline in incidence is, I am sure, due to the education of the public as to preventive methods and the more intelligent and modern procedures of therapy. Some years ago the second most common cause of death was due to tuberculosis, whereas today this condition occupies the fifth position. There is a definite decrease in the incidence of pulmonary tuberculosis which is the prime etiological factor in tuberculous salpingitis.

Figures from the Department of Health of the State of Maryland definitely support this opinion in regard to the white race but not so significantly in the Negro. In the years 1921 to 1925, the death rates per 100,000 population were 94.3 for whites and 281.4 for Negro. Now compare this to the figures for the five-year period, 1941 to 1945. We find a marked decline in the white race from 94.3 to 39.6 per 100,000 population; the decline in the Negro race is not so striking, namely 281.4 as compared to 184.7 per 100,000 population. The present death rate from tuberculosis in the Negro race is still too high but in spite of this there has been a marked decline in the incidence of tubal tuberculosis. The reason for this is difficult to ascertain.

Another aspect of the paper deals with recurrent attacks of pelvic inflammatory disease. These recrudescence attacks must be due to new infection from the urethra, cervix, or consort, or from increased viability of dormant cells in the wall of the tube. In 1921 Curtis carried out a rather exhaustive study on the viability of the gonococcus in the tubal wall and lumen with the resulting conclusions: "It has almost never been possible to obtain gonococci in culture from thoroughly ground Fallopian tubes removed from patients who have been free from fever and leucocytosis for a period of more than ten days or two weeks. The Fallopian tube appears, therefore, not to be a focus for chronic gonorrheal infection. Persistently active gonorrhea of the tubes is evidently ascribable either to recurrence from without or repeated invasion of bacteria from the chronically infected lower genital tract."

This opinion has prevailed for a number of years. However, in 1938 Studdiford studied this same problem and his findings did not support those of Curtis. His conclusions, based on a study of 24 patients with gonococcal salpingitis, were as follows: "Contrary to previous reports the Fallopian tubes may remain as active foci of gonococcal in-

months' pregnancy was found. The tumor had apparently ruptured previously as there was a small amount of dark watery fluid in the abdomen which may have accounted for the acute symptoms. The tumor was extensively adherent to the rectosigmoid which was pushed into the right side of the pelvis and lower abdomen. Four days after operation the patient was afebrile. She had an uneventful postoperative course. Here again the pre-existing pelvic tumor underwent some change inducing symptoms and signs of pelvic peritonitis which actually was responsible for recognizing the pressure of the malignant tumor. Actually the patient was admitted to the hospital for what was recognized as a pelvic inflammatory disease and after treatment with operation we determined the cause of the inflammatory process as a pre-existing adenocarcinoma of the ovary.

Discussion

There are many phases of this important subject which have not been discussed in this presentation. The large areas of loculated exudate, the difference in extent and consistency of adhesions observed at operation, the time and the indications for operation have not been mentioned. The purpose has been to focus the attention of this organization on this important problem and to try to think of it in terms so that medical students and house officers and physicians generally would understand that pelvic inflammatory disease is an entity because of anatomical and physiological characteristics of the female, but the inherent reaction of the individual to the process is not much different in the female pelvis than it is in other body structures. There may be some question about my suggestion that pelvic inflammation of non-infectious origin exists. Many of the accidents which occur in pelvic tumors, ectopic pregnancies, endometriosis will cause immediate reactions which are referred to as the phenomenon of shock, but if this reaction is not observed immediately or if this condition is not severe enough to warrant immediate treatment, an inflammatory reaction develops which is characterized by the stated symptoms and signs of pelvic inflammatory disease and if surgical treatment is instituted this fact will be demonstrated.

Summary

1. This presentation has been made with the idea of stimulating some interest in a very important gynecological problem.
2. I have tried to correlate it with inflammatory processes observed elsewhere in the body.
3. I have suggested that pelvic inflammatory disease is a reaction of the internal female genitals and their contiguous structures to some irritant.
4. The irritant may be either of bacterial origin or of physical origin.
5. Pelvic inflammatory disease is a term which has a definite connotation and should be used carefully.
6. I have indicated that the inflammatory processes of infectious origin develop by means of surface extension from a focus in the lower genital tract or by means of interstitial extension from a focus somewhere in the genitals or other body structures.
7. I have suggested that not all surface-extending infections are of gonorrheal origin since cultures and smears do not indicate the presence of these organisms.
8. Pelvic inflammation may be caused by changes in the status of pre-existing tumors and structures in the pelvis or physical changes in the structures of the pelvis and not be of infectious origin.

and other local pathogenic organisms. We have demonstrated this repeatedly by using the instruments contaminated by episiotomy for the removal of moles located elsewhere, with 100 per cent infection and destructive inflammation of these secondary wounds (the episiotomy wound healing promptly and with only the inevitable minor inflammatory reaction).

Moreover, the behavior of certain infecting organisms in the genital tract as compared with their behavior elsewhere must be remembered. It is necessary to mention only the trichomonads; the differences between the reactions to the gonococcus in the genital tract and in the joints; and the extraordinary behavior of *C. welchii*, which in the genital tract varies from innocuous infestation to extreme toxemia and death—with an extreme rarity of any major gangrenous process.

Finally, in the third phase of gynecic life, the lowering of resistance through atrophy, local anemia, and fibrosis is markedly greater than in any other part of the body.

DR. HARVEY B. MATTHEWS, Brooklyn, N. Y.—Dr. Mohler has reviewed in a very remarkable manner the question of pelvic inflammatory disease as we understand it, but whether we can agree with his bacterial or mechanical idea, as it were, we are not quite sure.

I have always felt and taught that pelvic inflammatory disease was due to infection of bacterial origin. We speak, very properly, of pelvic infections and think that as a result of such infections we have pelvic inflammatory disease. Just as in any inflammation we recognize the acute and chronic stages of the disease, every infection anywhere in the body must pass through these stages. It frequently happens, for the good fortune of the patient, that such infection clears up entirely due to the many factors controlling infectious processes in general, and the pelvis is left free of pathology. On the other hand, there is usually some residual pathology following these pelvic infections. Therefore, I cannot agree with the author when he says, "the term chronic is not descriptive of the process which follows acute attacks and should be used only when it refers to reactions such as those caused by tuberculosis, foreign bodies, and other slowly acting processes." Any bacterial or septic infection certainly does become chronic and may or may not leave in its wake some residual pathology.

Now, as to the pelvic inflammatory disease of nonbacterial origin, again I must disagree somewhat with Dr. Mohler. Of course, such acute inflammatory states do occur but they are complications secondary to some pre-existing pelvic lesion or tumor and are due to mechanical causes; e.g., ruptured ectopic ovarian cyst with twisted pedicle or degeneration of a fibroid due to interference of circulation to the tumor. In these conditions a correct differential diagnosis always gives the clue to the proper treatment, operative or conservative.

In conclusion, I believe that pelvic inflammatory disease is a well-recognized clinical-pathological entity caused by bacterial invasion and that what Dr. Mohler terms pelvic inflammation of nonbacterial origin is merely a mechanical complication of a pre-existing pelvic lesion or tumor. Of course, there may occasionally be infection also.

I agree most heartily with Dr. Mohler that pelvic inflammatory disease is a term which has a definite connotation and should be used with care and discretion, much more accurately than it oftentimes is.

DR. E. D. PLASS, Iowa City, Iowa.—More recently, the term "pleuropneumonia-like organisms" has occasionally invaded the literature dealing with pelvic infections in women, and, as more bacteriologists become familiar with this curious organism, the use of the term will become more common. This is particularly true since these organisms may develop by a process of pleomorphism from many gram-negative bacilli and cocci under the influence of extraneous factors, such as penicillin. Consequently, interpretation of its etiologic role in patients previously treated with this antibiotic is difficult or impossible.

Pleuropneumonia-like organisms or "L"-forms are evidently a part of the vaginal flora in many normal women, but thus far have not been implicated in vaginal infection. In our material representing cultures for 312 consecutive gynecologic admissions, there were 81

fections for long periods of time. Many cases regarded as acute exacerbations of chronic salpingitis may be due to recrudescence of residual infection rather than to reinfections."

With such divergent opinions existing we thought it worth while to restudy the problem. The selection of cases is important for we did not wish to subject young women with acute gonococcal disease to radical surgery when the condition could be alleviated in a large measure by the use of chemotherapy.

Our study is in its beginning and the majority of the patients studied are those with chronic salpingitis frequently associated with uterine fibromas. There is no debate as to the presence of organisms in the acutely inflamed tube but it is in the chronic conditions that there is a difference of opinion.

The technical procedure is as follows: A box with two glass sides is set up with an ultra-violet apparatus placed in the top. After an exposure of thirty minutes the air contained in the box is sterile as proved by cultures.

Smears and cultures from the lumen of the tubes are carried out in this sterilized atmosphere. Cultures are made on chocolate agar and incubated under 10 per cent carbon dioxide at atmospheric pressure. Sections of the tubal wall are macerated in a mortar using sterilized sand and sterile water.

To date one patient with subacute salpingitis and ten patients with chronic tubal disease have been studied bacteriologically. Six of these patients had associated uterine myomas. The patient with the subacute lesion showed positive gonococcal smears and cultures of the cervix and urethra while the tubes showed negative results on smear, cultures from lumen, and also cultures of macerated tube wall. Of the ten patients with chronic salpingitis, four showed no evidence of tubal infection. In the remaining six patients the tubes, cervix, and urethra were positive for gonorrhea on smear and culture and cultures of the macerated tissue. In one of these patients the examination of the cervix and urethra was not done.

It is obvious from this preliminary study that we can come to no definite conclusions as yet. However, it is clear that tubal infection persisted in six of the patients studied who had long-standing chronic disease. This is suggestive that the gonococcus may be present in the tube after acute symptoms have subsided and the condition has become chronic.

DR. WILLARD R. COOKE, Galveston, Texas.—I regret that I have been unable to obtain an adequate concept of Dr. Mohler's philosophy and ideas from a fifteen-minute condensation of so protean a subject. I gather that he includes the phenomena of repair, regeneration, and foreign-body reaction in his definition of inflammation, in addition to the true inflammatory reactions to trauma of mechanical, chemical, bacterial and protozoal origin. In any discussion of inflammation, the general and the peculiar local defense-mechanisms must be taken into account. I can agree that, in the preadolescent child, the phenomena of inflammation are probably identical with similar processes occurring elsewhere in the body. With the onset of adolescence, however, a great number of processes develop which are peculiar to the genital tract and modify greatly the behavior of inflammation. The vaginal epithelium, hitherto extremely vulnerable to noninvasive bacteria (and to trauma) becomes highly resistant. As normal physiologic processes various types of cyclic trauma occur, with inevitably resultant semi-inflammatory reactions, the creation of portals of entry, fluctuations in both general and local defense, etc. In the ovary there occurs the minor trauma of rupture of the follicle and the introduction of foreign bodies in the form of extravasated blood and of the dying and degenerating newly formed corpus luteum. In the uterus there occurs the frequent and considerable trauma of the loss of the endometrium, and the relatively infrequent but tremendous trauma incident to the termination of pregnancy. It is from the physiologically normal repair of these injuries that the controversy between the general and the gynecic pathologists in regard to "endometritis" has arisen. In the perineum there is evidently a specific local defense mechanism against the anorectal

The cases are presented as a part of this discussion to emphasize the need for more work on the etiologic relation of the "L"-forms to pelvic inflammatory disease in women. Since the organisms are resistant to penicillin, it is conceivable that they may be the causative agent in many penicillin-resistant infections in the female generative tract. It should furthermore be emphasized that the indiscriminate employment of penicillin may be producing pleomorphic variants of common bacteria, which have pathogenic properties and which cannot be controlled by penicillin.

DR. MOHLER (Closing).—I admit that I made an attempt to cover a rather large problem in a relatively short period of time. I tried to emphasize in my presentation that pelvic inflammatory disease needs reconsideration. I think Dr. Hundley brought that out in his discussion when he stated that the dictum that Curtis laid down in 1921 was not refuted until Dr. Studdiford made his presentation a few years ago. Dr. Cooke, I think, brought out a number of important points and I feel very positively that when patients are admitted to the hospital very often with a pelvic inflammation they have every sign and every symptom of pelvic inflammation but there is no evidence of infection which can be determined.

This problem needs to be considered and our whole conception of pelvic inflammatory disease I think needs reconsideration and a good deal of thought.

instances, 26 per cent, in which "L"-forms were cultivated. The figure agrees well with the few others reported in the literature. In addition, my associate, Robert J. Stein, was able to demonstrate the organisms in two cases of pelvic inflammatory disease, including one pelvic abscess, but is unable to interpret the findings with assurance.

The first case was in a thirty-year-old woman with a large acute pelvic abscess which had developed marked symptoms during the preceding week. On admission, Dec. 16, 1947, the temperature was 102.2° F. and soon rose to 104.4° F., the white blood count was 18,750 per mm. with 75 per cent polymorphonuclear leucocytes. Penicillin, 50,000 units, was given intramuscularly soon after admission but had little effect on the temperature. On December 18, posterior colpotomy released 300 c.c. of thick pus; a drainage tube was inserted. The temperature dropped promptly to 100.0° to 101.0° F. where it remained for 5 days, and then fell slowly to normal. She was discharged on Jan. 23, 1948, quite symptom-free, but returned to the outpatient clinic May 29, 1948, complaining of a dragging sensation in the right lower abdomen and slight fever. Both adnexa were thickened and slightly tender, and there was a golfball-size mass in the cul-de-sac. Aspiration of this mass yielded a few c.c. of bloody fluid.

The pus obtained at colpotomy revealed a pure culture of pleuropneumonia-like organisms, while the bloody fluid from the small mass aspirated five months later showed only *Bacteroides*. It is reasonable to assume that the pleuropneumonia-like organisms obtained in the first culture represented a pleomorphic variant of *Bacteroides* which later re-established its identity, but it is not clear whether the abscess was due to the pleuropneumonia-like organisms as such, or whether the original infecting agent had been *Bacteroides*, which had then under the influence of penicillin completed its pleomorphic change in the forty-eight hours before colpotomy. In any event, neither of these organisms is commonly considered in pelvic inflammatory disease, and yet it seems obvious that one or the other must have been the etiologic agent in this case.

The second case, gonorrheal pelvic inflammatory disease, represents more clearly the pleomorphic change. This 15-year-old girl had the correct diagnosis made by her home physician, who had prescribed some sulfonamide, which was taken for two days before admission on Feb. 16, 1948. There was evidence of acute gonorrheal salpingitis, and positive cultures for *Neisseria gonorrhoeae* were obtained on Feb. 16, 19, and 25, 1948. Upon establishment of the diagnosis, penicillin was administered intramuscularly in 100,000 unit doses every three hours for eight doses. On February 27, the day after conclusion of the penicillin therapy, a cervical culture revealed no gonococci but many colonies of pleuropneumonia-like organisms.

Pleuropneumonia-like organisms were first found in cattle and are now recognized as the cause of bovine pleuropneumonia. They are generally classified as bacteria, but in their pleomorphic development may produce forms that are filtrable and invisible. In contrast to the viruses, they can be grown on serum-enriched artificial media. The colonies are rarely visible and consequently are overlooked unless a special search is made under the low power of the microscope. The organisms are too fragile to permit study by usual methods and must be examined in the stained surface layers of solid media.

There is some confusion in the diagnosis due to the fact that pleomorphic forms of certain common gram-negative bacteria resemble the pleuropneumonia-like organisms so closely as to defy differentiation. This type of pleomorphism is evidently more common when other bacteria are subjected to the influence of penicillin. Consequently, it is impossible to determine the clinical significance of "L"-forms in patients who have been treated with this antibiotic.

In males, there is no reasonable doubt that pleuropneumonia-like organisms produce urethritis and prostatitis, but the place of the "L" forms in the etiology of pelvic inflammatory lesions in women is not so clear. Various authors have reported its occurrence in vagina flora of from 6 to 26 per cent of normal women, and in up to 75 per cent of those with pelvic inflammatory conditions. Dienes and his group report cultivation of the organism from six Bartholin abscesses and from two pelvic abscesses.

however, particularly with vascular disease, that these conditions do strongly predispose to a superimposed toxemia in the latter months of pregnancy. The high frequency of vascular disease (58 per cent) will be noted in the toxic cases of the above series.

It may well be that the same spasmogenic factor (pituitary and/or renal in origin?) which leads to permanent vascular changes and hypertension, is aggravated by pregnancy (through greater pituitary and/or renal secretion?) and causes greater tendency to spasm of the sphincters of the uterine veins, resulting in superimposed toxemia.

There is some justification for terming pernicious vomiting of pregnancy a toxemia, but it is not on the same basis as true toxemia of pregnancy. Reasoning from the greatly increased incidence of severe vomiting of pregnancy along with the marked increase in chorionic gonadotropin in hydatidiform mole, the effect of this hormone may directly or reflexly give rise to pernicious vomiting. It is probable, however, that toxic effects on the liver and kidneys are rather the result of starvation than of any inherent toxicity of the hormone itself.

Based on the foregoing clinical and pathologic evidences, it would, therefore, seem that there is but one toxemia of pregnancy, namely, that due to autolysis of placental tissue, whether it occurs in acute hemorrhagic infarction of the placenta or by necrosis of avascular hydatidiform villi imbedded at the placental site. The renal and vascular conditions commonly included among the toxemias of pregnancy are, in reality, only predisposing causes.

Is not the term "mild pre-eclampsia" a misnomer? The prefix "pre" certainly implies that eclampsia is about to occur, and if such is the case, neither the symptoms nor the findings can be mild. Many of these cases are vascular disease as shown by the retinal findings and the subsequent mild clinical course. The inference that pre-eclampsia will develop is erroneous, although it is strikingly frequent as seen in our own series.

On the basis of the foregoing evidence, the following would seem to represent the course and classification of true toxemia of pregnancy:

CLASSIFICATION OF TRUE TOXEMIA OF PREGNANCY

SUBACUTE HEMORRHAGIC PLACENTAL INFARCTION (SEVERAL WEEKS)	ACUTE HEMORRHAGIC PLACENTAL INFARCTION (SEVERAL DAYS)
1. Mild toxemia	1. -----
2. Moderate toxemia	2. -----
3. Severe toxemia	3. -----
4. Pre-eclampsia	4. Pre-eclampsia (may not be recognizable)
TERMINATION	
(a) Abruptio placentae	
or	
(b) Eclampsia	
or	
(c) Eclampsism	

The terminal conditions (a) (b) (c) are listed in the order of frequency. A practical gradation of symptoms and signs from Mild Toxemia to Pre-eclampsia is possible, but will not be detailed at this time.

were crowded and only three examining tables were available for a clinic of well over a hundred patients. Undoubtedly inaccurate diagnoses were made in a physical setup of this type that would not have been made had more adequate facilities been available. The new structure contains adequate beds, treatment rooms, and laboratory facilities, and a larger number of observation rooms. The latter are used for the direct admission of emergency cases and are air-conditioned, not a small factor in subtropical climates. Here a study of all acute diagnostic problems can be carried out thoroughly, comfortably, with adequate diagnostic aids, and immediate consultation from all divisions of the hospital staff, resident or visiting. An adequate number of residents are assigned to the division as well as full-time admitting physicians and in this manner emergencies are better cared for.

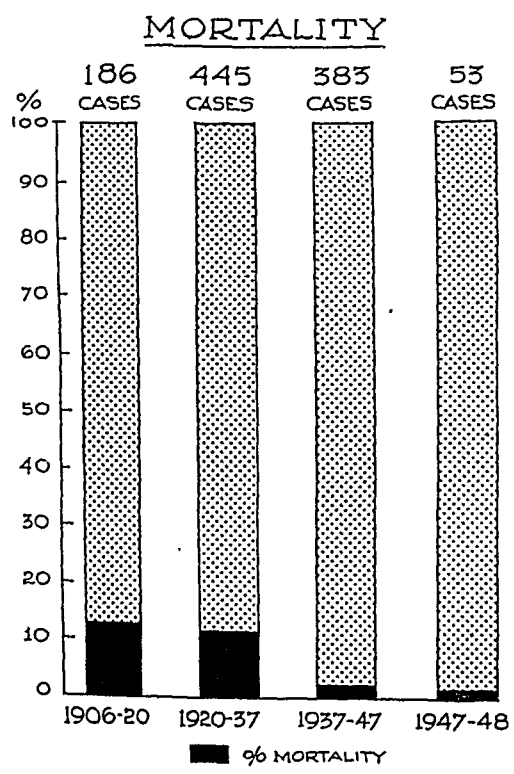


Fig. 1.

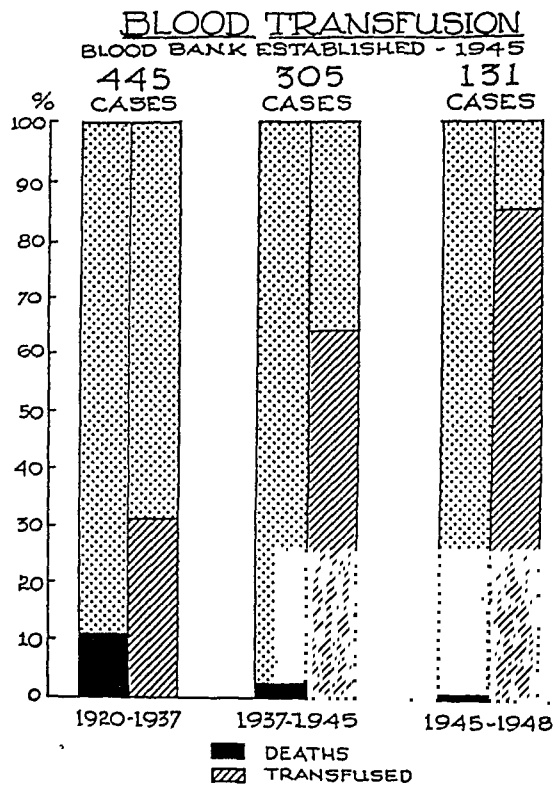


Fig. 2.

Staff

In 1937 residencies in the various specialties were established at Charity Hospital. Prior to this time the "house officer" system was in vogue, there being but two types of "house officer," i.e., medical and surgical. The surgical group cared for obstetrics and surgery while the medical group cared for other cases. The visiting staff were divided into specialty sections. Needless to say, the establishment of residencies in the various specialties, with strict designation of duties, has had much to do with the marked lowering of the mortality rate, especially since consultations among the different groups are easily sought and obtained. At about the same time, the hospital staff was reorganized and more wards brought under university supervision. For a long period there was only one university with a teaching service at Charity Hospital, now the hospital utilizes the services of two medical schools to supervise the care of 80 per cent of its patients. This has doubled the teaching

staff and resulted in the training of a larger number of men, in the various specialties, many of whom have remained on the staff of the hospital following completion of their residencies and this in a large part is responsible for the decreased mortality and morbidity rates.

Blood, Plasma, and Oxygen

There is no doubt that when a patient suffers from hemorrhage, the most efficient method of combating shock and other complications is the administration of blood in adequate quantities. Lyons and his workers⁵ have emphasized the importance of blood volume, not only as regards oxygen-carrying capacities but in combating infection. Furthermore, the demands by the body on protein to form hemoglobin, before the protein can be utilized to build body tissue, require the replacement of blood lost if good wound healing is to be expected. The liberal use of blood transfusions in cases of ectopic pregnancy is necessitated not only to combat shock but to reduce the possibility of infection, aid in the conquest of infection, and enhance the patient's chances of having a wound heal without dehiscence. Blood not only saves lives, it reduces morbidity. In the absence of available blood, plasma is a good substitute. The improvement noted in our mortality rate is in a large part due to the availability of plasma in 1938, dried plasma in 1944, and the establishment of a blood bank in 1945. In 1938 Graffagnino stated, "We feel hesitant about reporting the small number of transfusions which were given when we realize what a valuable therapeutic measure it is in this type of case. However, it must be appreciated that we are dealing with patients from all over the state of Louisiana, whose relatives are often difficult to contact for donors and when contacted are reluctant to give blood." This statement still holds true in some respects but the establishment of a blood bank in 1945 eliminated most of the difficulties we formerly experienced in obtaining blood.

From 1920 to 1937, only 31.5 per cent of the patients admitted with ectopic gestation received a blood transfusion and the mortality rate was 11.5 per cent. From 1937 to 1945, 64 per cent of the patients were transfused and a mortality rate of 3.3 per cent recorded. In the period, 1945 to 1948, following the establishment of a blood bank, 86 per cent of the patients with ectopic pregnancy were transfused, and the mortality rate decreased at the same time to 1.3 per cent (Fig. 2). In the years 1937 to 1945, 305 cases of ectopic pregnancy were observed at Charity Hospital and 354 pints of blood utilized for their care, an average of 580 c.c. per case admitted or an average of 750 c.c. per patient transfused. Since the establishment of the blood bank in 1945, to Jan. 1, 1948, 131 cases of ectopic pregnancy were admitted and 260 pints of blood administered to these cases, an average of 990 c.c. per case admitted, or 1,150 c.c. per patient transfused. Twice as much blood per patient admitted was used in the latter period as compared to the former. Not only were transfusions given, but in most instances as much blood, or more, than that found in the abdomen was utilized. In no instance was autotransfusion used. In a few cases overzealous and too rapid administration of blood, plasma, and/or electrolytes has resulted in transient overloading of the circulation and pulmonary edema. No deaths resulted, but in our efforts to replace or maintain blood volume the possibilities of introducing such an undesirable complication must be constantly kept in mind. At Charity Hospital the establishment of a blood bank and the increased use of blood transfusion in the therapy of ectopic pregnancy is a major factor in lowering the mortality and morbidity resulting from this pathological process.

A fair number of patients entering Charity Hospital with tubal pregnancies are admitted in shock or develop shock soon after admission. Graffagnino,³ commenting on his study of 445 cases of ectopic gestation admitted to Charity Hospital between the years 1919 and 1936 states, "There were 51 deaths in this series of cases. Twelve patients died before operation, five died on the operating table, and 34 died after operation. Of the patients who died, 35.3 per cent were admitted in shock, 25.4 per cent in poor condition, 17.7 per cent in fair condition and 21.4 per cent in good condition." Since 1937, 14 per cent of the cases have had shock on admission and an additional 7 per cent have developed shock soon after admission. Roughly, one out of every five patients was in shock before operation was started. The early administration of blood and/or plasma and early operation are musts in the treatment of intraperitoneal hemorrhage, but so, also, is the early and continuous administration of oxygen. Oxygen should be administered until the patient's blood pressure and pulse have been stabilized to or near to normal. Body cells, especially those of the more specialized organs, are sensitive to a deficient supply of oxygen. This is especially true of the pituitary gland of the pregnant female.⁶ The administration of oxygen has a twofold purpose, first, to help prevent death and, second, to help prevent those who do survive from being "human vegetables." Since 1937, the availability of, the generous supply of, and the early and continuous use of oxygen as a routine measure to patients in shock, has, together with blood transfusion and early operation, resulted in a marked lowering of the number of patients failing to survive operation.

Thirty-nine operative deaths recorded in the 51 deaths in Graffagnino's series were due primarily to hemorrhage and shock. In the twelve deaths that occurred since 1937, only two have been due to postoperative shock, even though approximately the same number of cases per year were admitted in this period in a state of shock or developed shock soon after admission, as is recorded in Graffagnino's series. There was no correlation between the amount of blood used per patient and the postoperative stay of the patient. This at first may seem paradoxical but in reality means that patients requiring transfusion were transfused in proper quantities, so that fewer complications developed and the postoperative stay was no longer than those in whom blood transfusion was thought to be unnecessary.

Diagnosis

Ectopic pregnancy presents a variety of signs and symptoms. None are constant. Certainly, in a patient giving a history of a missed period followed by sudden abdominal pain, while working or straining at stool, showing signs and symptoms of shock and in whom one is able to palpate a tender abdomen, tender cervix, and doughy mass in the cul-de-sac, the diagnosis is not difficult. However, unfortunately, very few cases fall into this category. In the majority of cases the symptoms and signs follow no set pattern.⁴

In this series, from 1906 to 1920, the diagnosis was mentioned on admission to the hospital or operating room in 45 per cent of the cases. From 1924 to 1935, in only 63 per cent of the cases. From 1937 to 1942 in 70 per cent of the cases. From 1942 to 1947, it was mentioned in 83 per cent of the cases, whereas in 1947 ectopic pregnancy was mentioned in 94 per cent of the cases. The absolute diagnosis of ectopic pregnancy, that is, an unequivocal diagnosis without mention of any other pelvic lesion was 40 per cent in the period of 1906 to 1920, 60 per cent in 1924 to 1934, 55 per cent in 1937 to 1942, 63 per cent in 1942 to 1947, and 74 per cent in 1947 (Fig. 3). Coincident with the

drop in mortality rate there has been a decrease in the time from admission to operation and also in postoperative stay. Certainly any diagnostic procedure that is fairly specific should help. We do not for one moment doubt that better facilities, increased trained personnel, and blood and oxygen have been important cogs in lowering the mortality and morbidity rate on our service but we also believe that the early routine use of cul-de-sac puncture in all cases suspected of having eecyesis has been one of the more important factors involved. The diagnosis is established earlier, with certainty, and operation is performed sooner. We have not seen any disadvantage or complications from the procedure. We believe that ectopic pregnancy should be treated by immediate operation as soon as the diagnosis is confirmed.

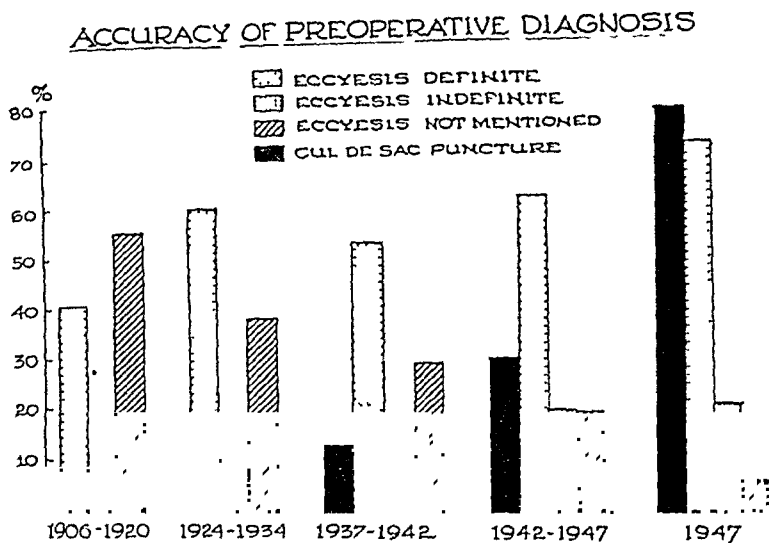


FIG. 3.

From 1920 to 1937 only 7 per cent of the patients were operated upon within three hours of admission and less than 30 per cent within 24 hours. Gradually the number of patients operated upon soon after admission increased until, in 1947, 60 per cent of the patients admitted were operated upon within three hours and 83 per cent within 24 hours (Fig. 4).

Immediate operation was made possible by the early specific diagnosis of intra-abdominal bleeding. Earlier diagnosis of intra-abdominal bleeding in turn was accomplished by the almost routine use of cul-de-sac puncture in all cases suspected of having eecyesis. Many of our staff in former years were certain that they could ascertain by vaginal examination the difference between blood in the cul-de-sac, either encysted or not, and pus or serous exudate. This is possible in many but not all cases. Routine examination of exudate in the cul-de-sac by means of needle puncture has led to the diagnosis of many cases of unsuspected ectopic pregnancies, and the discovery of pus or serous exudate in many cases where extrauterine gestation was suspected or believed to exist without doubt. The procedure is now used routinely on our service. True, in a few instances cases of unruptured tubal pregnancy have been missed and false positive or false negative punctures have been encountered but in no instance has a death resulted. The very fact that cul-de-sac puncture has been utilized in cases of unruptured ectopic gestation means that the possibility was in mind and these patients were either held

in the hospital for observation or told to return home but on the first sign of increased pain or bleeding, or feeling of faintness to return immediately. Moreover, all of these patients have their blood typed, cross-matched, and the Rh factor determined, in order that, if an ectopic pregnancy exists and has not been diagnosed, when rupture does occur blood will be available immediately. The possibilities and potentialities of culdoscopy in the latter types of cases are being explored on our service by two of us (W. D. and D. B.) but as yet no specific answer as to its value has been crystallized in our mind.

TIME INTERVAL FROM ADMISSION TO OPERATION

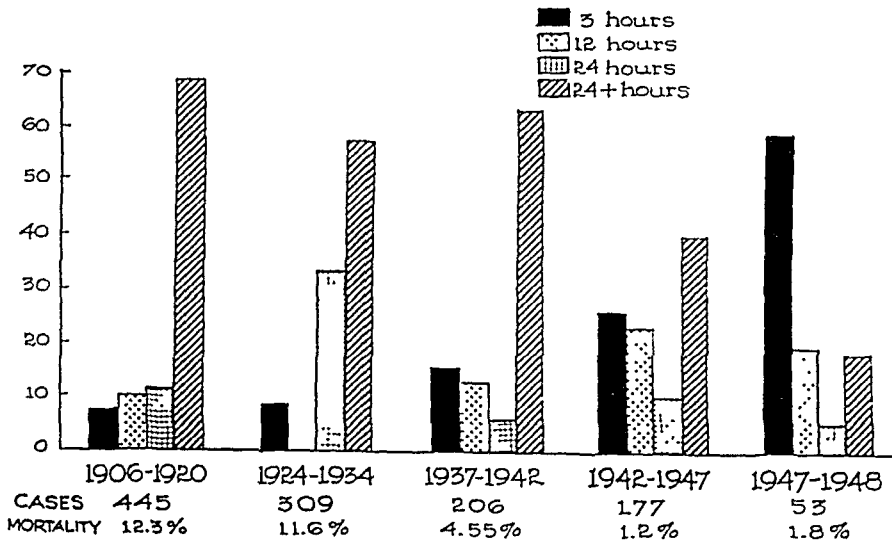


Fig. 4.

We have not used, though many large clinics do, colpotomy in the diagnosis or therapy of ectopic gestation. Colpotomy is used by us only when an abscess points in the cul-de-sac, whether the abscess is an infected hematoma or not. Early diagnosis is a very important factor in reducing the mortality and morbidity arising from ectopic pregnancy and exploration of the cul-de-sac either by needle puncture, culdoscopy, or colpotomy accomplishes this end.

Operation

Early diagnosis and early operation should mean decreased mortality and morbidity and shorter hospital stay. Our procedure is to operate upon cases of tubal pregnancy as soon as the diagnosis is established and the operating room can be made ready. Patients in shock or near shock are administered oxygen and transfused as soon as grouping, cross-matching and Rh typing can be performed. Whether the patient is in shock or not the operation is begun as soon as possible. We do not believe that we accomplish anything by transfusing a patient and having the blood eventually find its way into the peritoneal cavity. In intraperitoneal hemorrhage the bleeding vessel must be ligated. In eccyesis we are dealing with shock from hemorrhage and the patient will not recover from shock until the source of bleeding is controlled. If the source of bleeding is not controlled surgically, she probably will succumb. Of the 88 fatal cases of tubal gestation occurring at Charity Hospital from 1906 to 1948, twenty (12 per cent) died from intraperitoneal hemorrhage and shock without any operative procedure having been undertaken. Cases of eccyesis can and do hemorrhage to death within the peritoneal cavities and

are emergencies. Blood transfusion without immediate operation is no guarantee that the patient will survive until "she is a better operative risk." No one should be lulled into a sense of false security simply because transfusion has been started. We have seen patients die of ruptured tubal gestation while being "prepared for operation with blood transfusion."

Operative Procedure

The objective in the surgical management of ectopic pregnancy is to control intra-abdominal bleeding. Once this has been accomplished, removal or reconstruction of any organ or organs is potentially hazardous to the patient and in each case where such is contemplated the gravity of the measure or measures projected must be carefully considered by the surgeon. The seriousness of the incidental pathology, the condition of the patient, the amount of blood encountered in the abdomen, the quality of the anesthetic, the availability of compatible blood, and the extended scope of the projected operation must be carefully weighed. The procedures utilized in 424 cases of ectopic gestation operated upon from Jan. 1, 1937, to Jan. 1, 1948, are outlined in Table I. In no case can any of the fatalities encountered in this period be ascribed to surgical procedures used in addition to that necessary to control hemorrhage. It is re-emphasized, however, that in the vast majority of cases the operative procedure should be limited solely to the measures necessary to control the hemorrhage. Unilateral salpingectomy or salpingo-oophorectomy was the procedure of choice in 76.6 per cent of the 424 cases operated upon. One hundred seventeen surgeons, the vast majority residents, managed the cases in this series.

The anesthetic administered should be determined by the condition of the patient. Seventy of the 424 operative cases had spinal anesthesia. The remainder were anesthetized by ethylene, cyclopropane, or ether following gas induction. In no instance could a death be attributed in any way to the choice of anesthetic.

TABLE I. OPERATIVE PROCEDURE AND MORTALITY

CASES		SURVIVED	DEAD	TOTAL
Unilateral salpingectomy		134	3	137
Bilateral salpingectomy		16	0	16
Salpingo-oophorectomy		189	0	189
Hysterectomy				
Subtotal	47			
Total	14			
Vaginal	4			
		65	0	65
Salpingectomy and suspension		20	1	21
Not operated upon		0	8	8
Total		424	12	436
Incidental appendectomy—42 cases—no deaths				

Postoperative Care

The reduced postoperative stay and decrease in morbidity and mortality not only reflect better preoperative and operative care but improved postoperative care as well (Fig. 5). Since 1937, chemotherapeutic agents and antibiotics have been added to our armamentarium. In addition a better understanding of adynamic ileus and the postoperative physiologic requirements of these patients has done much to hasten recovery. Patients in whom a large amount of blood is found in the abdomen usually develop a postopera-

tive ileus, no matter how gently the operation is performed or how little the pelvic organs are disturbed. The prophylactic use of Wangenstein suction for forty-eight to seventy-two hours in such cases has done much to insure rapid and complete recovery. Since 1937, in 436 cases it was found advisable or necessary to decompress 51 patients (10 per cent) either prophylactically or because of postoperative ileus. The efficacy of this policy aided by the early and judicious use of chemotherapeutic agents and antibiotics, when fever developed postoperatively, is established in that only two patients died from peritonitis in the period 1937 to 1948. Both these patients had peritonitis on admission. In Graffagnino's series, 1906 to 1920, thirteen of twenty-three deaths (57 per cent) were found to be due to peritonitis or "toxic ileus."

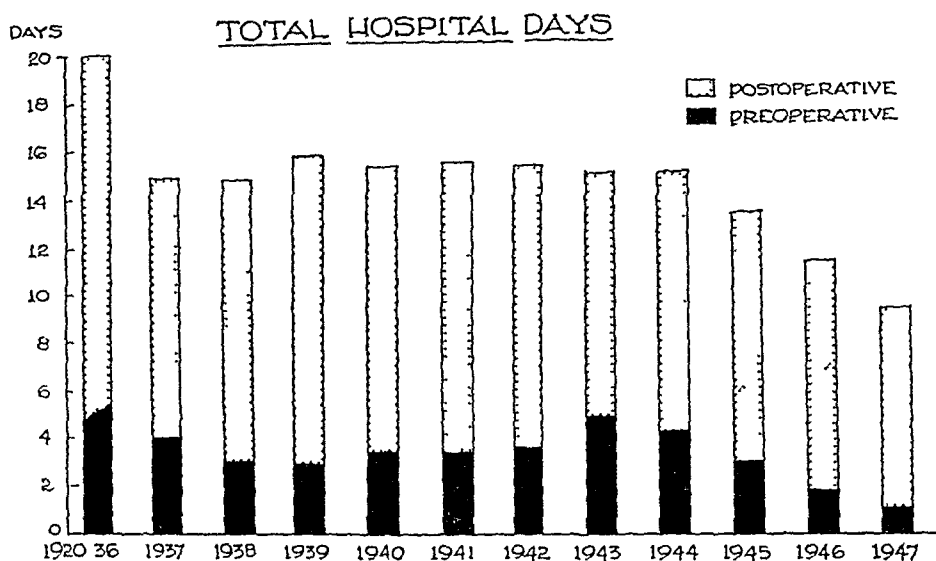


Fig. 5.

Evisceration of wounds most often occurs in malnourished, anemic patients, who, besides being depleted in protein and vitamins (especially vitamin C), develop distended abdomens and/or severe coughs. The prevention of, or early treatment of, adynamic ileus by the prophylactic or therapeutic use of Wangenstein suction; the liberal use of blood transfusion to replace lost blood volume and to lessen the demands on administered protein to produce hemoglobin and thereby increase available protein for fibroblastic production; and the intravenous administration of vitamin C and protein hydrolysates until the patient can tolerate food by mouth have been of inestimable value in that no case of evisceration, irrespective of type of suture material or type of wound closure, has been observed since 1937. True, five cases of the 436 (1.2 per cent) had some separation of the skin edges of the wound and in some the subcutaneous fat tissue separated, though none were severe enough to require secondary suture nor was fascial separation noted.

Wound infection was noted in 9 per cent of the cases operated upon since 1937. Phlebothrombosis, thrombophlebitis, or suppurative pelvic thrombophlebitis have not developed in any case observed since 1937.

Deaths

Of the twelve patients who expired, eight died without benefit of surgery. Death resulted from cerebral apoplexy in one case of a 6 months' intrauterine gestation, and an old, inactive, tubal pregnancy was an incidental finding at

autopsy. The remaining seven patients died of massive intraperitoneal hemorrhage. Three of these expired within a few minutes following their arrival at the hospital. In all, procrastination on the part of the patient and not of the physician was responsible for the demise. Of the remaining patients who expired without surgical therapy one died in the admitting room after remaining there one hour and forty-five minutes without receiving blood or being prepared for surgery. Another died of shock en route to the operating room five hours after admission and, although the admitting diagnosis was correct, blood was not available for this patient. Because of inaccurate diagnosis, two others died ten hours and forty-eight hours, respectively, following admission, even though repeated transfusions were utilized in the latter. These four cases we consider to have been preventable deaths. Of the four patients who died following operation, two expired shortly after surgical therapy. Both of these were admitted, in extremis, their abdomens filled with blood and though they received prompt, thorough management, the outcome was fatal. Another patient expired twenty days after operation from intestinal obstruction. One patient had peritonitis resulting from an infected tubal pregnancy on admission and died shortly after laparotomy. Though some of these deaths were preventable in many they were the result of the patients' own procrastination in seeking medical care and resulted in their being admitted in an extremely serious state or moribund condition.

Conclusions

1. The mortality rate from ectopic pregnancy in the years 1906 through 1936 fluctuated between 11.4 per cent and 12.3 per cent. From 1937 to 1945, 2.7 per cent fatalities were encountered. In the years 1945 to 1948, a further reduction to 1.7 per cent was accomplished.

2. Better physical facilities, the establishment of a residency system, and improved educational programs were instrumental in lowering the mortality and morbidity.

3. The establishment of a blood bank with the subsequent increased availability and use of blood is a major factor in the better results observed.

4. A better understanding of shock and postoperative physiologic requirements is reflected by the lowered number of fatalities and complications.

5. The increased use of cul-de-sac puncture and aspiration has increased the percentage of accurate and earlier diagnosis and is another major factor in the betterment of results obtained.

6. Ectopic pregnancy is an emergency. As soon as the diagnosis is established the pathological process should be treated by immediate surgery.

7. No other surgical procedures should be performed except that necessary to control the intra-abdominal hemorrhage, unless the patient is in excellent condition.

8. In cases suspected of having an unruptured ectopic gestation the patient should have her blood group and Rh type determined in order that should ecyesis be present and rupture ensue valuable time will not be lost in administering blood.

9. Many fatalities result from tubal pregnancy that might not have occurred had the patient sought medical care earlier.

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Discussion

DR. FREDERICK J. LYNCH, Boston, Mass.—It is stated that extra-uterine gestation occurs once in every 300 pregnancies and a gauge of its importance as a cause of maternal mortality is evident in glancing at the statistics reported by Williams and Corbit of Philadelphia. In the ten-year period 1931 to 1940 it caused every eighteenth death in Philadelphia, every sixteenth death in New York City, and every twelfth puerperal death in Chicago.

One factor which influences the mortality statistics in any series of cases, and over which we have little control, is the all-important interval between the occurrence of the rupture or abortion and the time of entrance to the hospital, caused by tardiness on the part of the patient to call the doctor and the reluctance of the patient or indecision of the attending physician to have immediate hospitalization.

As Dr. Collins points out, there are two main types of cases, the typical and atypical, the typical accounting for 40 per cent of the cases and atypical 60 per cent. The former requires no diagnostic acumen but it is the latter that causes difficulties, and the delay for observation is the factor that results in trouble and causes the morbidity and mortality figures to mount, in any series. These atypical cases frequently are associated with a heterogeneous group of signs and symptoms which tend to raise the question in the mind of the physician of things other than an extrauterine pregnancy. The one note, however, that seems to sound through all these bizarre groups of symptoms is a woman exposed to pregnancy, who has menstrual irregularity in conjunction with pelvic pain, and a history and physical examination which are equivocal. This patient should be promptly hospitalized and subjected to the routine workup as outlined by Dr. Collins and immediately operated upon as soon as the diagnosis is established.

Although not mentioned by Dr. Collins, we have found that the biologic test—either an Aschheim-Zondek or Friedman—is helpful but the results must be interpreted. A positive test is an important addition to the diagnostic data but does not exclude the possibility of an atypical interrupted intrauterine pregnancy. It should be remembered that the test determines the presence of live trophoblast from which the anterior pituitary-like substance causing the positive test is produced. It must also be realized that false positives can be caused, rarely, by chorionepithelioma, leiomyosarcoma, corpus luteum cyst, and granulosa cell carcinoma. If the trophoblastic tissue has disintegrated and disappeared, the test will be negative, a condition which occasionally obtains in the presence of an old ruptured extra-uterine pregnancy and occasionally even in recent ones. The positive biologic test can be of distinct value in arriving at the diagnosis but only when correlated with, and supported by, the other signs, symptoms, and findings of ectopic pregnancy. A negative test in the presence of a doubtful diagnosis may occasionally justify temporizing.

Also, a falling blood picture which seems to be incommensurately lower than the amount of external bleeding is extremely suggestive of hemorrhage into the abdominal cavity or extravasation into its tissues, and the presence of slight icterus in these patients is an almost infallible sign of hemorrhage into the peritoneal cavity.

Unquestionably, the most valuable single diagnostic aid is cul-de-sac aspiration or colpotomy. The patient, in whom an extrauterine pregnancy is a possibility, should have a needling of the posterior cul-de-sac using a large size needle—a needle which will permit the passage of fibrin and small clots. The presence of old blood in the barrel of the syringe is considered as positive evidence and its absence a negative test for extrauterine pregnancy. The old blood is identified by its characteristic brownish color, the lack of viscosity and its inability to clot. If blood is not found and the diagnosis is still in doubt the posterior cul-de-sac may be incised and each tube examined separately.

Burch and Seitchik report 37 cases suspected of harboring an extrauterine and in which cul-de-sac puncture was done; there were no false negatives and two false positives—one an adenocarcinoma of the cul-de-sac, and the other a ruptured Graafian follicle. In the series of cases they reported the test was 94.6 per cent accurate which compared very favorably with a correct diagnosis rate of 65 per cent in 34 cases in which the diagnosis was arrived at by the other usual clinical and laboratory means.

There has been a steady improvement in the mortality statistics associated with extrauterine pregnancy throughout the country. This has unquestionably been a part of the general improvement in all operative figures and is also probably a reflection of the immediate availability of appropriate blood, the vast improvement in the choice and administration of suitable anesthetics, and a more or less standard order of procedure as to the surest and most expeditious manner of arriving at the diagnosis.

DR. COLLINS (Closing).—Time did not permit me to make reference to the work of Dr. Frank Whitacre of Memphis in the study of blood hemachromogen in ectopic pregnancy. I think Dr. Whitacre has developed a very valuable diagnostic test, applicable not only to ectopic gestation, but to any case of intra-abdominal bleeding. We are very much impressed, even though we have only a small series, so far 40 cases, with the results obtained.

One thing we did not bring out was our management of the suspected unruptured ectopic. These patients are all matched and typed so that if the diagnosis is correct and they do rupture, we can give them blood immediately.

In the process of autolysis of acute hemorrhagic placental infarcts, it is probable that histamine is produced earlier than guanidine, very much as, in fractional distillation, a certain distillate comes over at a certain temperature, and another at a higher temperature. This may account for a higher incidence of abruptio placentae than eclampsia.

While the opinions expressed in this discussion seem to be dogmatically stated, a sincere endeavor has been made to theorize only to the extent justified by the placental pathology, correlated with the placental circulation and the clinical course. If it should direct thinking and research into paths which to us seem more promising, the effort will be deemed worth while.

Conclusions

1. The frequency with which signs and symptoms of toxemia precede abruptio placentae, the occasional simultaneous occurrence of abruptio and eclampsia, and the identical findings at necropsy, are generally accepted as evidences that abruptio placentae is a manifestation of toxemia.

2. The occasional occurrence of fulminating abruptio without prodromal symptoms or signs of toxemia, has heretofore prevented unqualified acceptance of abruptio as a part of toxemia.

3. The consistent finding of acute and subacute hemorrhagic placental infarction in fulminating abruptio, identical with those found in fulminating eclampsia, plus evidence that the primary site of hemorrhage in abruptio adjoins the site of infarction, furnish additional evidence indicating that abruptio is a part of toxemia of pregnancy.

4. A spasmogenic factor (pituitary and/or renal?) acting on the sphincters of the placental veins probably initiates the following sequence of events: (1) obstruction to the outflow of fetal blood from the dependent unit of placental tissue, (2) distention, thrombosis, or rupture of the villous vessels with resulting enlargement and crowding of villi, (3) diminution of maternal and absence of fetal blood supply to villi from crowding and thrombosis, (4) dissemination of the poisonous products of the resulting placental necrosis with development of symptoms and signs of toxemia.

5. True toxemia of pregnancy of gradual development (several weeks or more) progresses through stages of mild, moderate, severe, and pre-eclamptic toxemia.

6. True toxemia of pregnancy of fulminating development (several days to one week), outstrips characteristic symptoms and signs and reaches the severe or pre-eclamptic stage at once. The lagging symptoms and signs may not appear until the early days of recovery.

7. Severe toxemia or pre-eclampsia terminates in any one of three ways: (a) abruptio placentae, (b) eclampsia, and (c) eclampsism, in this order of frequency. Occasionally (a) and (b) occur simultaneously.

8. Renal and vascular disease are not true toxemias but are predisposing causes, probably through a spasmogenic factor (pituitary and/or renal?) which may cause overaction of the sphincters of the placental veins with resulting acute or subacute hemorrhagic placental infarction and superimposed toxemia.

Layer 3.—Comprises a cross section of the cervix, the vaginal canal, and the vaginal orifice with its attachments to the levator muscles. The vaginal support is connective tissue coming from the white lines and their extensions and inserts itself into the vaginal wall. The vagina does not have to depend on the bladder, the cervix, or the rectum for support.



Fig. 1.—Shows the model with the layers closed. All five layers are in contact and can be opened. In the upper four layers, the muscle tissue is smooth, while in the lower or fifth layer all muscle tissue is striated.

Layer 4.—Comprises the rectum from the sacrococcygeal junction to where it passes through the sphincter ani externally. The rectum is held in an enveloping tensile sheath of fascia endopelvina which folds posteriorly to form its mesentery. Connective tissue arises from ischiococcygeal ligaments, passes to the rectum, gives it support, and keeps it in position.

Layer 5.—Comprises the levator muscle, which is wholly striated. The muscle can be divided into six component pairs of bands (one band from the left side meeting its corresponding band from the right side to move an organ in the sagittal plane of the pelvic floor). These bands in order, from front to back, move:

1. The vaginal wall under the urethra (Fig. 3)
2. The lateral walls of the vaginal orifice (Fig. 3)
3. The perineal body
4. The anus
5. The raphe
6. The coccyx.

Each component pair can function apart from another pair or in concert with it. The levator components have origin in the white line, are striated

KNOW THE PELVIS*

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(From the Woman's Hospital of New York)

K NOW THE PELVIS is a challenge to clarify our knowledge of the supports of the genital organs. By a simple model, one can clearly show where the damages of labor occur. Such information will point the way to an improved restoration of position and function, of organs long partially disabled.

Blood vessels, nerves, lymphatics, and pelvimetry are not included in this paper, nor are sinuses, fistulas and other pathologic conditions.

Backache, prolapse of organs, incontinence of urine and feces, poor voiding and evacuation are all sequelae of: (a) subinvolution of the uterus with or without retroversion; (b) infection of the cervix, and, (c) hidden injuries during labor. The pelvic organs (uterus, cervix, ovaries, tubes, bladder, urethra, vagina and rectum, anus and levator muscles) are all suspended from the white lines and their extensions along the ischiococcygeal ligaments over the coccyx.

This supporting body can be represented by a band and the attached structures can be divided into five superimposed separable layers (Fig. 1). Each of the four upper layers consists of a part of, or the whole of, an organ, held in position by supports which consist of connective tissue alone or connective tissue mixed with smooth muscle only (Fig. 2). One end of this support is attached to the white line and the other to the individual organ. The fifth and lower layer consists entirely of striated muscles. They have their origin in the white lines on each side and their insertions into or near the sagittal line of the pelvic floor and they move the urethra, the vagina, the perineal body, the sphincter ani, the raphe, or the coccyx either in separate units or in concert. This structure anatomically is the levator ani muscle.

Layer 1.—Comprises uterus, bladder, ureters, ovaries, and tubes. They are covered and supported by fascia endopelvina, of thickness to vary the strength necessary to accomplish delivery of the fetus without dislodging the organs. The round, uterosacral, and pubovesical ligaments are not attached to the white lines. This fascia endopelvina is attached to the white lines and their extensions, and makes an almost complete diaphragm between the abdominal cavity above and the extraperitoneal cavity below. It is completely covered with peritoneum.

Layer 2.—Comprises a cross section of the cervix and its supports. The outer half of the support coming from the white lines is entirely connective tissue, while in the inner half the connective tissue becomes increasingly more smooth muscle and less connective tissue, until at the cervix the support is predominately muscle. The cervical support makes a shelf for the bladder, the ureters, and the uterine and vesical blood vessels.

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By distention, the cervix is transported about 2 inches toward the promontory of the sacrum. The lateral view shows where the bladder, the cul-de-sac, and the rectum lie. When radioactive elements are used to treat the cervix or uterus, and the vagina is distended with packing, damage may occur to the sigmoid, and even to the ileum.

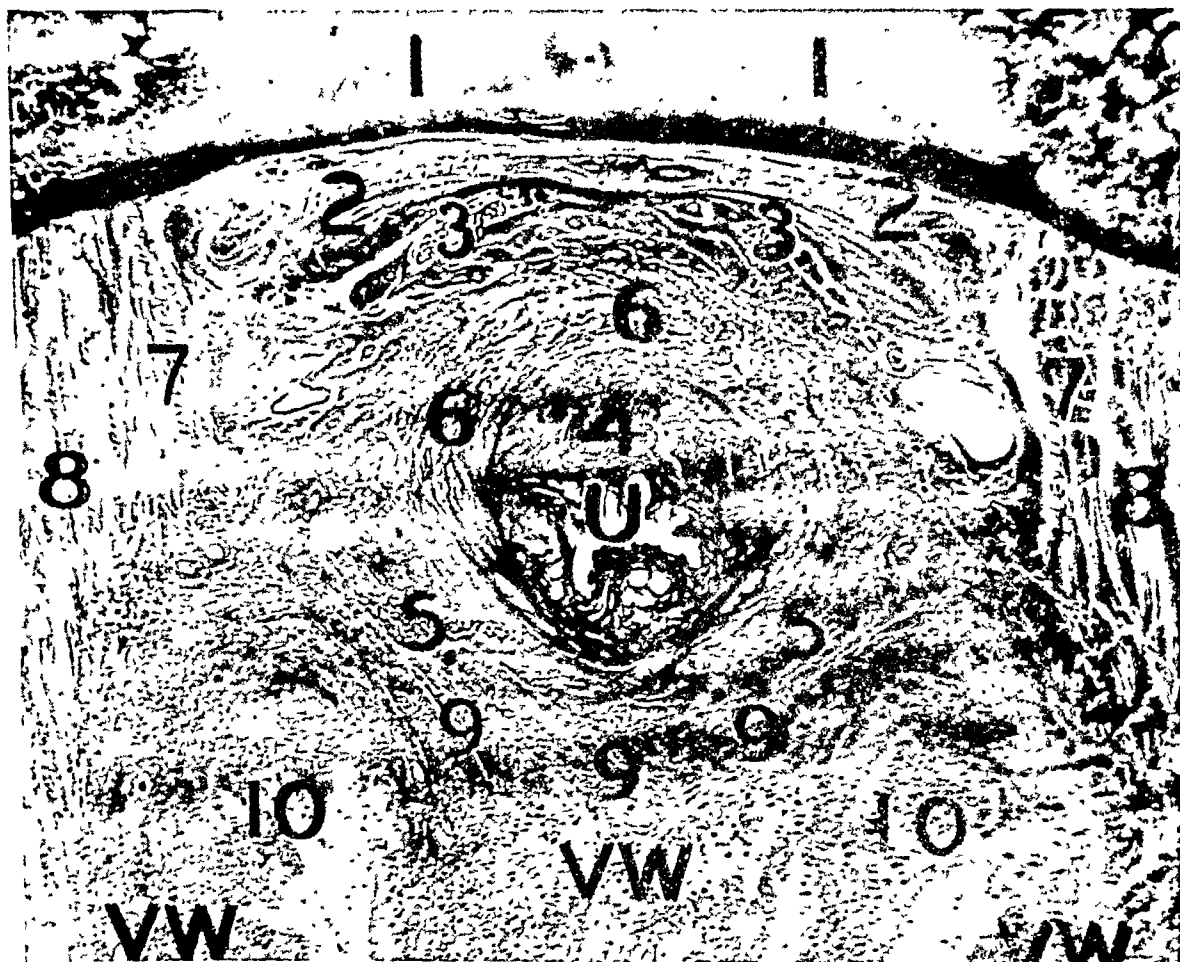


Fig. 3.—A histological section, cut at right angles to the axis of the urethra, showing the urethra, the levator muscles, the dimples, and the vaginal wall. The symphysis pubis is cartilagenous. The urethra is attached to it by connective tissue (its only fixed portion). The levator urethrae muscles with both origins and insertions are shown, as are similarly, the levator vaginae muscles. One sees how the dimple is formed. The anterior vaginal wall and the wall of the urethra are fused. A portion of the muscle of micturition appears, and from its thickness one can appreciate its strength. The letters and figures on the photograph designate:

- U Urethra
- VW Vaginal wall
- 1. Symphysis pubis (cartilagenous)
- 2. Attachment, urethra to symphysis
- 3. Urethral vessels (enter near attachment)
- 4. Circular smooth muscle, urethra
- 5. Longitudinal smooth muscle, urethra
- 6. Part of the muscle of micturition (striated)
- 7. Levator urethrae muscle
- 8. Levator vaginal muscle
- 9. Fusion vagina and urethra
- 10. Dimple.

Cleavage Planes.—There are only two cleavage planes bordering on the vaginal wall (where the adjacent organs are held loosely to it by areolar connective tissue). One plane, the vesicovaginal, lies between the bladder and vagina

muscle, have sheaths and have insertions into organs. They have a maximum length which is quite liberal and equal to the length of the sheath in extension. The insertions are loosely held together when away from the sphincter and are endowed with a great range of separation to prevent laceration when the fetus passes through the pelvic floor.

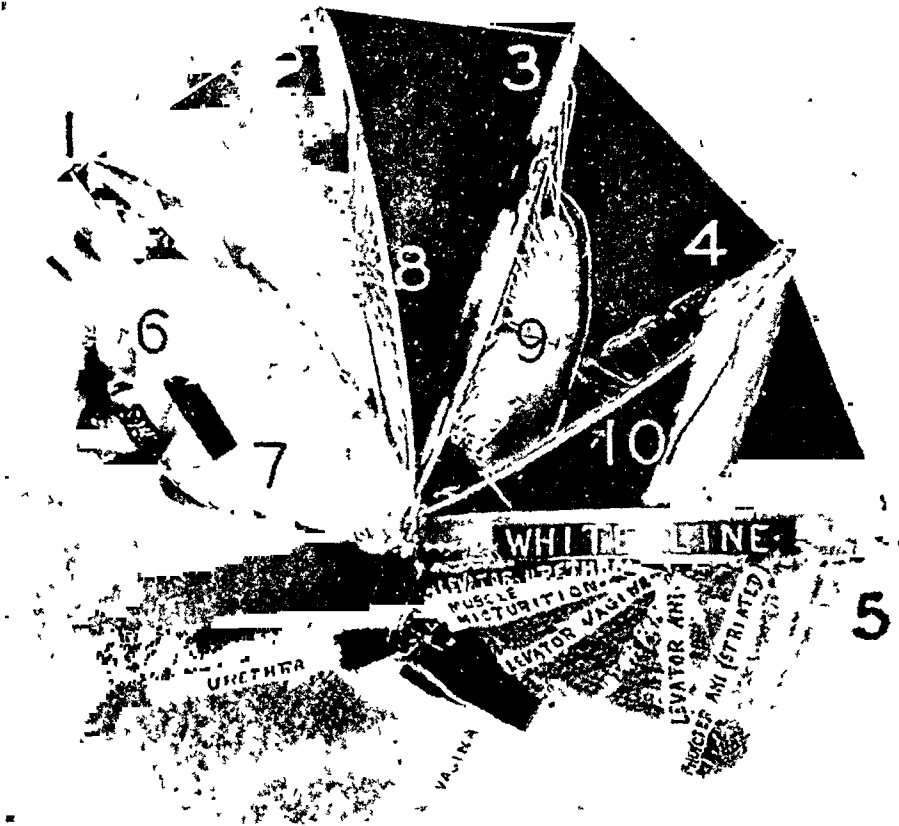


Fig. 2.—Shows the same model with the layers separated. As in the paper, the "white line" is the basic structure. Layers 1, 2, 3, and 4 are opened up, and layer 5 is shown below the "white line" in this illustration. The numbers designate:

- 1, 2, 3, 4, and 5. Layers
5. Levators muscles
6. Uterus
7. Bladder
8. Cervical supports
9. Vagina and supports
10. Rectum and supports.

The sphincter ani muscle bears the same relation to the levator ani muscle as the cuff to the sleeve of a shirt. The sphincter ani muscle, also striated, has two functions:

1. To pull together the insertions of all the levator components which make up the pelvic floor, and
2. To cut off voluntarily the evacuation of feces by compressing the sphincter ani internal (smooth muscle).

The Vagina.—Normally the collapsed walls are in contact and the cervix bears a certain relation to the line joining the heads of the femurs. A fully distended nulliparous vagina (Fig. 4) holds about 180 c.c. fluid (3 per cent sodium iodide). A piece of metal is placed in the external os of the cervix. X-rays are shown (superimposed) and indicate the position of the cervix: 1. in relaxation; 2. bearing down; 3. traction; 4. with vagina fully distended.

and through it good supporting tissue to restore and repair the bladder and vagina can be reached, and the other plane, the rectovaginal, lies between the rectum and vagina, and through it good supporting tissue of vagina and rectum can be reached to repair and restore any of these organs displaced by labor injury.

First Stage of Labor.—The cervix commences to dilate, the cervical and vaginal supports loosen until the cervix and attached vagina reach the white line. The uterine contractions exert a pull on the cervix until the greatest plane of the fetal head passes the white line. If the first stage of labor is long, its length and intensity should be given as much consideration as the second stage. There are indications in current literature that, in labor, the uterine muscle is very active near the cornua, and that the cervix and lower uterine segment are comparatively passive.

Second Stage of Labor.—The second stage begins with the first pushing pain and marks the transfer of the pull of uterine contractions from the cervical rim to the attachment of the levator muscle to the vagina. If pudendal block analgesia has been selected, now is the time to give it, so that the levator muscles will not impede the passage of the head through the vaginal canal. Pudendal block seems to accelerate the descent of the occiput posterior head. Close observation should be kept to see that the anterior vaginal wall (with the bladder above) is pulled up over the head. If not, a Deaver retractor should be placed between the fetal head and the cervix, the vaginal wall, and the bladder and urethra.

As the head presses on the pelvic floor, the striated muscles stretch but have limited elongation, and, once this limit is reached, something has to give way for the head to pass. Here the prophylactic episiotomy (median) prevents: 1. Concealed damage to the levator muscle insertions moving the urethra and vaginal orifice; 2. concealed damage to the levator muscle insertions moving the perineum; 3. concealed damage to the inner margin of the sphincter ani muscles.

The author much prefers median episiotomy. He can find the incised fascia better and hence do a more satisfactory repair.

Third Stage of Labor.—This stage should not be rushed. If no interference has been used in the first stage and in the first half of the second stage, usually damage to the cervix is small and there is not much bleeding. If bleeding continues, all possible sources are explored. The cervix, sulcus tears (anterior, posterior, and lateral), and the episiotomy incision should be examined. Repairs of sulcus tears are done by approximating the full depth of the faces of the tears with interrupted No. 00 plain catgut sutures. The repair of the levator, the sphincter ani, and Colles' fascia are all accomplished by approximating the fascia only with continuous No. 00 plain catgut. Fig. 6 greatly clarifies our understanding of the rectum and one can learn from it the significant ideas necessary to a simple repair of a third-degree laceration.

Post Partum.—Normal examination is made on discharge. The patient is advised to urinate frequently in order that the uterus will get a chance to take the normal position. At four weeks post partum, the patient is again examined to determine the extent of involution of the cervix and uterus. At this time about 25 per cent of the patients have a markedly patulous cervical canal filled with mucus. The uterus is frequently retroverted and the patient's general condition seems below average. The mucus is removed from the cervix and the canal is packed with applicators saturated with Negatan or 10 per cent solution of silver nitrate. One week later, the patient is much better, the cervix almost closed, nearly free of mucus, and about 30 per cent of those who had postpartum

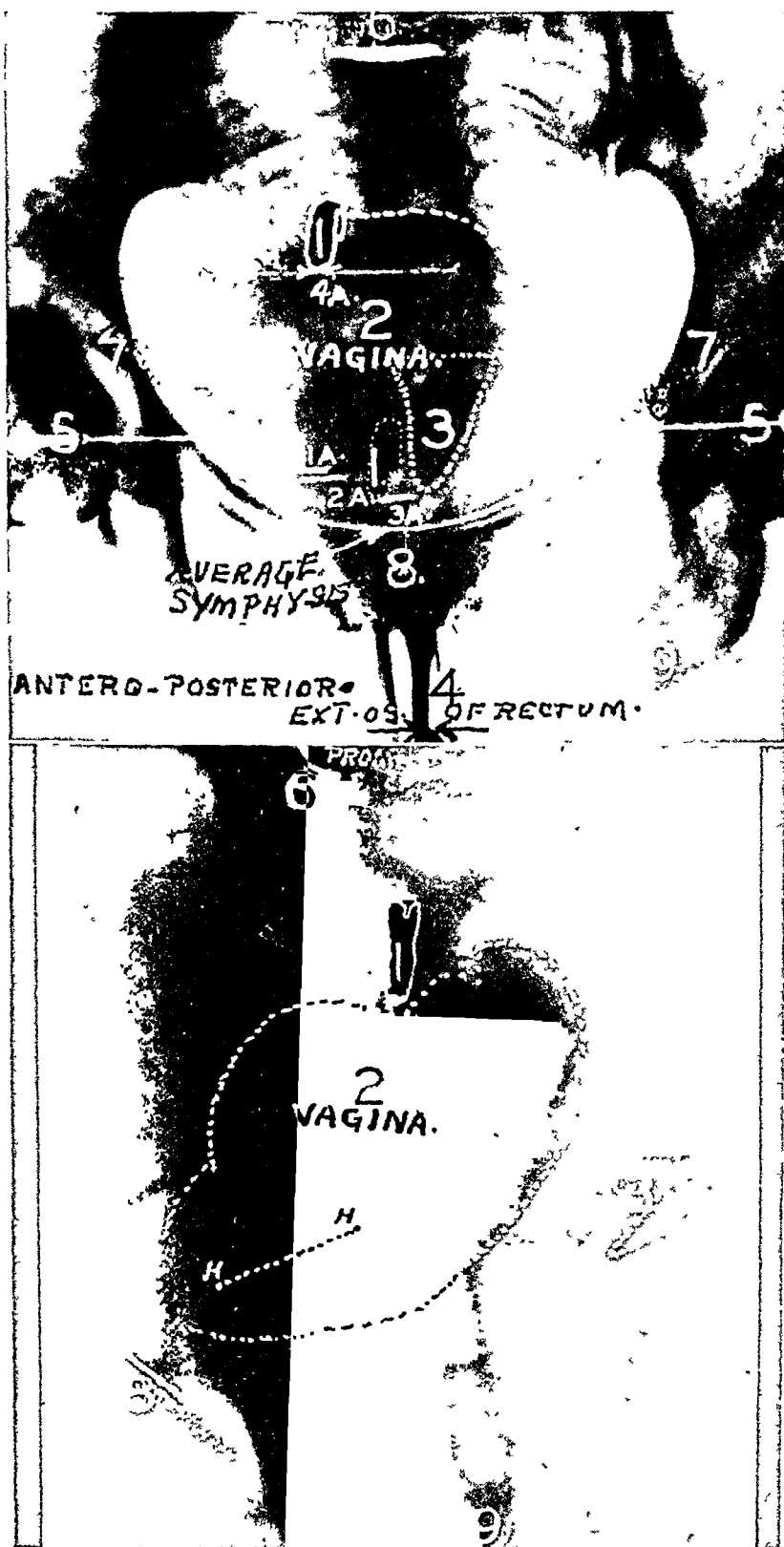


Fig. 4.—Shows the x-ray of a nulliparous vagina fully distended with 180 c.c. of a 3 per cent solution of sodium iodide. The anterior-posterior view appears above, the lateral view below.

- 1 A. Position of the external os of the cervix when the patient was relaxed.
- 2 A. Position of the cervix when bearing down.
- 3 A. Position of the cervix when under traction.
- 4 A. Position of the cervix when the vagina is distended.

Also shown are: 2. Vagina, 3. Coccyx, 4. Anus (external os of the rectum), 5. Heads of the femur, 6. Promontory of the sacrum, 7. Ischial spines, 8. Symphysis, 9. Tuberosity of the ischium.

A uterus and cervix in prolapse after menopause should be removed and all accompanying plastic repair done. Great care should be taken to free the urethra of all adhesions and to pull the ends of the levator urethrae snugly under the urethra. Great care should be taken to repair a laceration of the

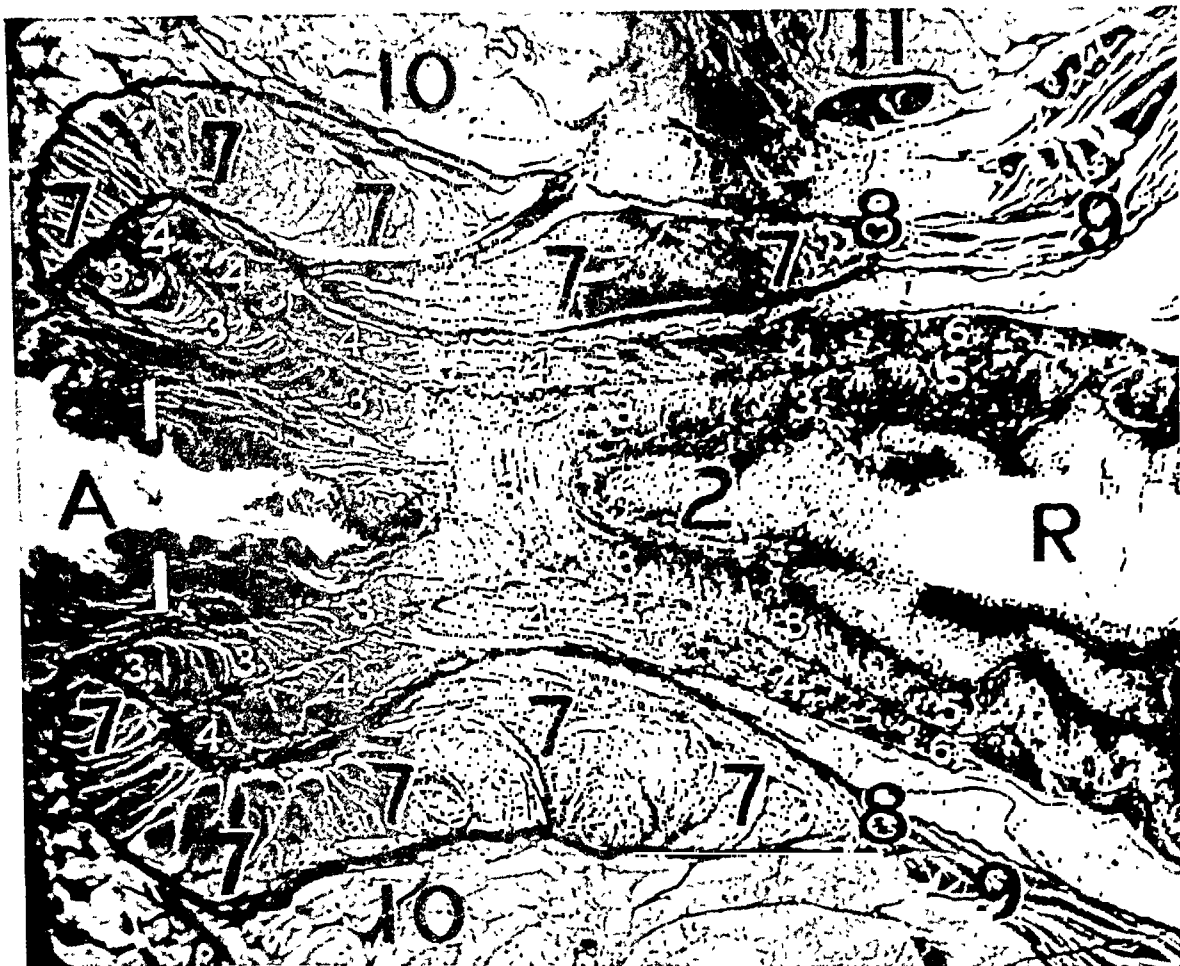


Fig. 6.—A histological section cut through the rectum, the plane being at right angles to the sagittal plane and through the axis of the sphincter ani. One can recognize the external sphincter ani muscle (striated) on either side of the canal, and its junction with the levator ani muscle. To consummate the ideal repair of a third-degree laceration, one must suture the opposite junctions together. The internal sphincter ani muscles (longitudinal and circular, smooth) are easily identified. Also shown are the pudendal vessels, the ischioanal fossae, the rectal mucosa, the anus and the rectum. The letters and numbers on the photograph designate:

- A Anus
- R Rectum
- 1. Anal mucosa
- 2. Rectal mucosa
- 3. Circular anal muscle (smooth)
- 4. Longitudinal anal muscle (smooth)
- 3 and 4. Sphincter ani internal
- 5. Circular rectal muscle
- 6. Longitudinal rectal muscle
- 7. External sphincter ani (striated)
- 8. Junction sphincter and levator ani muscle
- 9. Levator ani muscle (striated)
- 10. Ischioanal fossae
- 11. Pudendal vessels.

perineum by approximating the keypoints, junction of levator to sphincter ani muscles) and then approximating all other fascial layers with No. 00 plain catgut sutures (Fig. 6).

retroversion now have the uterus in place. This procedure has paid dividends in end results.

Prolapse.—The prolapse of the uterus and cervix only appears here. When a cervix is amputated, as in a Fothergill operation, prolapse is mostly relieved. Labor with poor involution of the uterus and cervix together with cervical infections contributes most frequently to prolapse. Prolapse of the cervix and uterus frequently drags down the kidneys and the ureters, and, after the uterus and cervix have been removed, and the prolapse corrected, the kidneys rise to an almost normal level (Fig. 5).



Fig. 5.—Shows one roentgenogram of the bladder, the ureters, and the replaced prolapsed uterus and cervix, superimposed on a second roentgenogram of the bladder, and ureters which was made after operation for prolapse (the cervix and uterus being removed).

S. Sound in uterus, one end attached to cervix, C.

Before indicates the level of the kidneys before operation and shows the extent of their prolapse.

After indicates their level after operation which is normal.

Repairs.—All damages to the cervix should be repaired immediately after delivery. If one sees a new patient who has a cervical laceration with a healthy cervical mucosa, extensively exposed to the vagina, the cervix should be repaired.

9. When the uterus and cervix prolapse, the bladder, ureters and kidneys are all pulled down. When the prolapse is relieved, the kidneys return to their normal level.

10. The junction of the levator ani muscle and the sphincter ani muscle is a crucial point. When divided in episiotomy, they must be approximated after delivery to accomplish a creditable repair.

11. All repair of levator muscles, sphincter ani muscles, perineal muscles and Colles' fascia must be consummated by approximating their sheaths after episiotomy. In secondary repair, scar tissue must be removed.

12. Restoration of partially destroyed or displaced structures must be accomplished by attaching them to good supporting tissue coming from the white line and this restoration must be *maintained*.

The author wishes to express his appreciation to those members of the staff of the Woman's Hospital, who, by argument, suggestion, or discussion, have made this contribution possible.

930 PARK AVENUE

Discussion

DR. WILLIAM F. MENGERT, Dallas, Tex.—My interest in the supportive function of the pelvic fascias began in 1933 following a prolonged discussion with a member of this Association concerning so simple a question as, "What holds the uterus in place?" Since we could not agree, I devised an experiment to test the question. If all the structures attached to the uterus are severed one by one in a fresh cadaver, during which process a constant downward traction is applied to the cervix, those structures contributing most to uterine support will manifest themselves. The experiment was conducted during the course of post-mortem examination on each of nine fresh female cadavers with anatomically normal genitals. It was clearly demonstrated that the tissues surrounding the cervix and the upper vagina supported *both* organs. In other words, not only paracervical, but also paravaginal tissues contribute to uterine support. The slight amount of support contributed by the sacrouterine "ligaments" stems from the fact that they are condensations of the paravaginal tissues. Actually, they are not true ligaments.

Especially noteworthy in the cadaver experiment was the total lack of support from the round ligaments and other structures attached to the region of the uterine fundus. When extensive second-degree prolapse was produced experimentally, the round ligaments hung in lax curves and were not drawn tight, despite the uterine displacement. Normally, the round ligaments are not uterine suspenders and do not function in maintenance of habitual ante- or retroversion. We know they are essentially muscle tissue, that they hypertrophy during pregnancy, contract with the uterus during labor, originate at the fundus, and insert in the vulva. Perhaps their sole function occurs during labor, to prevent the uterine fundus from "backing away" from the vulva.

Forty and more years ago, Tandler taught that the normal uterus is a movable organ. In 1936, Harris, Mengert, and Plass demonstrated with bimanual examination that it alters its position in response to postural change. The experiment was conducted on twenty young women with normal pelvic viscera, but confined to bed with pulmonary tuberculosis. Diddle, Mengert, and Earl in 1939 confirmed this response of the uterus to postural change by objective demonstration on normal women, and women with prolapse, by means of roentgenograms and superimposed photographs.

In the light of the foregoing, and of clinical experience, it is difficult for me to accept the belief that failure of involution produces an exhausted, below-par woman with a backache and partial prolapse. It is difficult for me to believe that subinvolution of the uterus is fre-

All muscular repairs can be perfectly accomplished when corresponding fascial edges are approximated. For ideal secondary repairs, these fascial edges must be denuded of scar tissue, visualized, and meticulously approximated to obtain a result possessing good function and minimum scar tissue.

Comments and Conclusions

1. Undernutrition of every patient must be corrected first, if we expect to get optimum healing and commendable end results.

2. This gynecological and obstetrical study has been made to elucidate the relation of the genital organs and their supports to the white lines, the ischiococcygeal ligaments, and the coccyx. The structures have been divided into five layers. The upper four layers are composed of the genital organs, their muscles and connective tissue supports, all muscle tissue being smooth. The fifth, and lowest layer, is composed entirely of striated muscles.

3. In Layer 1, postpartum retroversion, an associated subinvolution of the uterus, or an indolent cervix, together with an infrequently emptied bladder in some patients, creates a problem. Treating the cervix from the fourth to the sixth week post partum and having the patient urinate on schedule will pay good dividends in end results.

4. Prolonged subinvolution of the cervix and uterus and infection of the cervix in time lead to lengthening of the cervical and vaginal supports; prolapse begins, falling of kidneys and bladder follow, and unrecognized or concealed labor damages appear, together with a train of unexpected symptoms.

5. Sulcus vaginal tears nearly always damage rectal supports and frequently injure some division of the levator muscles and contribute to a patient's misery.

6. *Labor:* The first stage duration should be accorded as much serious attention as the second stage. The first pushing pain is a critical time in labor. At this time (a) the fully dilated cervix is pulled up over the maximum plane of the fetal head; (b) the pull of the uterine contractions is transferred from the cervix to the levator muscles attached to the vaginal orifice; (c) the pudendal block, if this method of delivery has been selected, should be commenced; (d) forceps can now be applied with little damage to the cervix and lower uterine segment, but not necessarily to the vaginal canal supports; (e) prophylactic protection of the cervical rim, the anterior vaginal wall, and the urethra can profitably be carried out by placing a Deaver retractor between the cervix and the head and leaving it there until the head reaches the pelvic floor. Prophylactic conservation of the urethra, the vaginal orifice, and the levator muscles can be accomplished by the median episiotomy made sagittally through the perineal body to facilitate an easy delivery of the head.

7. Working familiarity with the two lines of cleavage will be a great asset in getting satisfactory results in all plastic repairs.

8. The vagina distends in the second stage of labor to have a diameter nearly three times the size of the distended nulliparous vagina.

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1259 CLIFTON ROAD, N. E.

Discussion

DR. RALPH A. REIS, Chicago, Ill.—Dr. Bartholomew's solution of the problem of abruptio placentae, eclampsia, and toxemia of pregnancy is intriguing. Careful study of the complete report was both stimulating and provocative for it represents a different approach to an understanding of the etiology, pathology, and course of all three conditions. Dr. Bartholomew and his group find that toxemia of pregnancy frequently precedes abruptio, that abruptio and eclampsia occasionally occur simultaneously, and that abruptio and eclampsia have identical necropsy findings. They consistently find hemorrhagic placental infarcts in fulminating abruptio and fulminating eclampsia and believe that the primary site of the hemorrhage adjoins the site of infarction. They further postulate a spasmogenic factor acting on the placental vein valves, thus producing obstruction to the outflow of fetal blood, followed by distention, thrombosis, necrosis, and rupture of the villous vessels, thereby causing toxemia from the poisonous products of placental necrosis.

In our experience, about 60 per cent of patients with abruptio show toxemia, 8 per cent give a history of trauma, and 32 per cent have neither. Furthermore, the severity of the abruptio does not seem to be proportional to the severity of toxemia. There have been 402 instances of toxemia at Michael Reese Hospital during the past ten years. During the same period there have been 18 instances of eclampsia, none of which had any evidence of abruptio, and 83 cases of abruptio with no evidence of eclampsia. Eclampsia and abruptio do not seem to be as closely linked as the essayists believe. Furthermore, the State of Georgia has five times as much eclampsia (1.56 per cent) as does the State of Illinois (0.31 per cent), but has less abruptio (0.72 per cent) than does Illinois (0.8 per cent). It would seem, therefore, that the majority of toxemias show no evidence of abruptio and that the simultaneous occurrence of abruptio and eclampsia is so uncommon as to be accidental.

The necropsy findings of eclampsia include periportal necrosis of the liver. This is pathognomonic of eclampsia and we have not found these liver changes following abruptio. Neither have we found changes in other organs which could be considered the same for both abruptio and eclampsia. The single exception is glomerulonephrosis of varying degree—a condition which cannot be considered pathognomonic or even characteristic. We have been unable to find hemorrhagic placental infarcts in all cases of abruptio and eclampsia. It is most difficult to differentiate between hemorrhage into the placenta and recent hemorrhagic infarct. The placenta is a highly vascular structure and differentiation is always difficult in richly vascularized tissue. To me, infarction means necrosis of tissue as a result of interference with the blood supply. In many of the slides shown, the normal cell architecture is still present and the cell nuclei seem normal both in configuration and staining reaction. This raises the question as to whether this represents hemorrhage into the placenta rather than hemorrhagic infarcts.

quently a forerunner of prolapse of the cervix. I do not think that it is necessary to empty the urinary bladder every three hours, or that retroversion will result if more than eight ounces of urine remain in the bladder for long periods of time. We have greatly simplified our puerperal care. Women are allowed to get out of bed to go to the bathroom as soon as they are conscious. In consequence, catheterization of the puerperal woman is virtually unknown. On the gynecologic ward, we pay no attention in the average patient to the concept of residual urine. Our routines include catheterization only for distress. These, and many other simplified measures, have been successfully applied on our wards to numbers of thousands of obstetric and gynecologic patients.

I do not think that lengthening of the round and uterosacral ligaments has anything to do with the occurrence of retroversion. I do not think that it is either necessary or desirable to protect the anterior vaginal wall with a Deaver retractor during the expulsive stage of labor.

Kantor, working at Parkland Hospital, recently studied the urinary bladder during labor by means of roentgenograms and indwelling rubber balloons attached to a pressure recording system. He established, beyond peradventure of doubt, that after the fetal head descends into the bony pelvis maximum pressure on the urinary bladder at the height of uterine contraction is but a few millimeters of water, and that our worries regarding potential danger to the urinary bladder during spontaneous labor are not well founded.

DR. HAROLD L. GAINES, Kansas City, Mo.—The mandate in the title, "Know the Pelvis," is one, by the author, to himself, which he hopes will attract others. His detailed histologic studies on the muscle of micturition previously reported and this paper are testimonials to his sincerity and qualifications to do so.

In this discussion he has broadened the scope to include not only the concept of the pure anatomist but has included the dynamic aspects involved in the processes of pregnancy, parturition, and the puerperium. These less fixed phases are far more difficult to understand and interpret because of their complex variables. For example, the influence of ethnic characteristics demands that we use some restraint in our effort to control the end results of parturition by what may be ill-advised and damage-producing procedures. They should also temper our reports of accomplishments. The American Negro, although neglected by trained specialists in obstetrics, survives with less damage than the European races.

McKelvey states that the greatest number of prolapse cases is around Manchester, England, and that it is rare in China. Reis states that Jewish women have a high incidence, while Torpin, Findley, and others report a high incidence of spina bifida occulta in women with uterine prolapse. Within races there is evidence of genetically controlled variations similar to the almost 100 per cent family history of varicosities of the extremities.

The essayist states, "Many a woman is left with a retroversion she did not have before pregnancy because we obstetricians have neglected to help many of our postpartum patients finish up the involution of the cervix, uterus, and supports from four to six weeks after delivery. Consequently, she remains below par, has backache, and goes about exhausted for months, ending up with partial prolapse of the uterus and cervix some years later." Our impression is that the retroversion more likely is a "symptom" accompanying the other complaints and in many instances corrects itself spontaneously as observed, requiring at most the temporary use of the pessary only as a part of general hygienic measures. This we do, and have without proof the impression of benefit.

The procedure recommended at one month post partum, of removing the normal alkaline protective plug of mucus with application of irritating drugs making possible the invasion of ever present pathogens, to me is questionable. The physiologic changes, requiring 280 days of gestation, that make parturition a near normal physiologic process, are not reversible in a precipitous fashion. Eight weeks will accomplish this as a functional fact but not anatomically in a good per cent; twelve to sixteen weeks are required in some, depending on factors of general health, diet, and demands upon the body as a whole.

The next remark that aroused interest was, "Many a woman has had the levator support of her urethra torn and this predisposes to a relaxed urethra with incontinence." This observation we have recorded occurring in 5 per cent of primiparas and 28 per cent of multiparas. Of these, 16 per cent of the primiparas and 7.3 per cent of the multiparas had stress incontinence. Our studies have further suggested, not only because of damage in this area but because of the results noted throughout the vagina with cystocele, rectocele, and vaginal prolapse, that we give thought to the physiology of the second stage of labor and prevent or minimize the damage associated with it.

The first stage of labor is well respected by most, the second and third stages find many interfering with the normal mechanism. There is no more reason to doubt the efficiency of this physiologic mechanism than that of the first stage. I am sure there would be less damage if operative interference in the second stage were less radical and along a physiologic pattern.

The intrinsic weakness of the vaginal supporting structures follows a law of embryologic oncology that prevents any hollow viscus from developing a firm fascial sheath, thereby permitting normal functions of coitus and parturition. Hormonal influences and chronic passive congestion bring about enough softening to make parturition possible with a minimum of damage to this vulnerable area. Further, there is a uterovaginal mechanism in the second stage that cannot be denied its place as a protective factor to the vagina against the advancing fetus.

This uterovaginal mechanism is accomplished at complete dilatation by progressive shortening of the uterine musculature and cervical connective tissue fibers. This shortening, by drawing high out of the pelvis the external os with its attached vagina, gives counter pull against the advancing fetus. Our practice has been, when using outlet forceps, to apply them between contractions and exert traction only during the height of a contraction. At the early stages of perineal distention a mediolateral episiotomy is done to prevent further elongation of the vagina, damaging its attachments posteriorly to urogenital diaphragm and endopelvic fascia covering the levators and to prevent circumferential stretching that might injure the urogenital diaphragm and levator attachments anteriorly supporting the urethra.

We reviewed our statistical studies in an effort to arrive at an explanation for the acquisition of cystocele, rectocele, and detachment of the urethra. Multiparity was considered because of the increase over primiparous patients and two factors suggested themselves: one the precipitous nature of the second stage and the other the increase in the size of the baby. In the primiparous patients with detachment of the urethra the length of labor was longer, confirming the opinion of others that pressure and ischemia are factors.

✓ A REPORT ON THE CESAREAN SECTIONS DONE IN ST. VINCENT'S HOSPITAL, NEW YORK*

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(From the Department of Obstetrics and Gynecology)

BECAUSE of the increased prominence of this operation and the resultant widespread interest, a survey made of all the cases of cesarean section in one institution should provide some interesting data and conclusions.

This report includes all the cesarean sections, 536 in number, performed on the obstetrical service at St. Vincent's Hospital, New York, during the first fifteen years of the operation of this service, from 1932 to 1946, inclusive. It includes both private and ward cases. The total number of deliveries during this period was 15,429, and the incidence of cesarean section was 1:29. Of the total number of deliveries, 6,414 were private cases and 9,015 ward cases. The incidence of cesarean section was consistently higher in the private cases (1:17) than in the ward group (1:57). There were 297 low flap sections, an incidence of 55.4 per cent; 215 classical, 40.1 per cent; 16 extraperitoneal operations, 3 per cent; and 8 hysterectomies, Porro, 1.5 per cent. There were ten maternal deaths, all in the classical operation group, a mortality of 1.86 per cent of the total cesareans.

The operations were done by thirty-two different operators, twenty-five of whom were members of the attending staff and seven of the courtesy staff.

The incidence is shown in Table I. It is arranged so that the rate per hundred cases each year is given in the private and ward cases. There is a steady rise from 1.5 and 3.4 to 2.7 and 6.9, respectively.

The high incidence may be the result of judgment on the part of the obstetrician or the demands of the patients for the safety of their babies; nevertheless, with the high incidence we are always confronted with the possibility of a higher maternal mortality. The relationship between incidence and mortality in this series has not, however, been affected by the rapid rise in incidence.

There were more than twice as many cesareans performed on the private patients as on the ward patients. The main reason for the higher course of the upper curve in the table has been the arbitrary choice of cesarean section in the private case. Some obstetricians have deliberately chosen cesarean section in preference to the vaginal delivery in their debatable cases. No doubt anxiety about the private case has been the deciding factor in their choice. Some men trained in abdominal surgery, who do relatively few obstetrical cases, perform a cesarean as the easiest way out of a dilemma. Moreover, consultations do not always safeguard proper indications in some cases, as is so ably expressed by Hawks when he says "they [the consultants] are often merely politely agreeable."¹

*Presented, by invitation, at the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 9 to 11, 1948.

INCIDENCE OF CESAREAN SECTIONS RATE PER 100 DELIVERIES PER YEAR

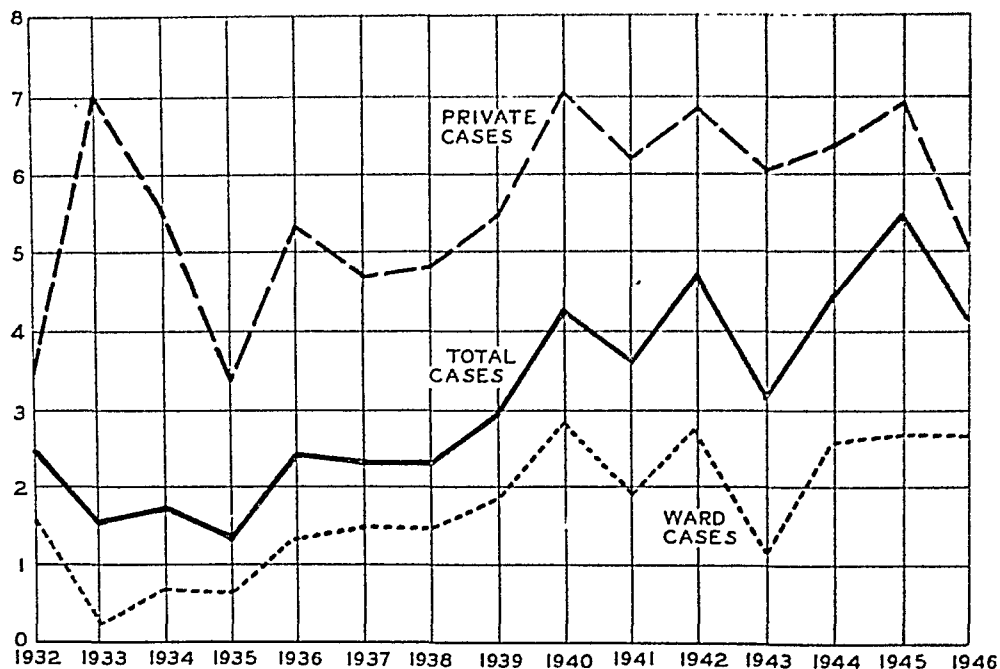


Fig. 1.

TABLE I

INCIDENCE OF CESAREAN SECTIONS IN WARD AND PRIVATE CASES

YEAR	TOTAL DELIVERIES			CESAREAN SECTIONS			INCIDENCE OF CESAREAN SECTIONS		
	TOTAL	WARD	PRIVATE	TOTAL	WARD	PRIVATE	TOTAL	WARD	PRIVATE
1932	121	63	58	3	1	2	1:40	1:63	1:29
1933	525	425	100	8	1	7	1:66	1:425	1:14
1934	750	588	162	13	4	9	1:58	1:147	1:18
1935	820	610	210	11	4	7	1:74	1:152	1:30
1936	739	532	207	18	7	11	1:41	1:76	1:19
1937	815	604	211	19	9	10	1:43	1:67	1:21
1938	934	685	249	22	10	12	1:42	1:68	1:21
1939	807	549	258	24	10	14	1:34	1:55	1:18
1940	870	572	298	37	16	21	1:24	1:36	1:14
1941	1,000	615	385	36	12	24	1:28	1:51	1:16
1942	1,251	654	597	59	18	41	1:21	1:36	1:14
1943	1,845	1,104	741	58	13	45	1:32	1:85	1:16
1944	1,647	826	821	73	21	52	1:22	1:39	1:16
1945	1,365	481	884	74	13	61	1:18	1:37	1:14
1946	1,940	707	1,233	81	19	62	1:24	1:37	1:20
TOTAL	15,429	9,015	6,414	536	158	378	1:29	1:57	1:17

Indications

The various indications for the cesareans are listed in Table II. Many patients had several indications, and these are classified according to the major indication in each case.

TABLE II. CHIEF INDICATIONS FOR CESAREAN SECTION

Contracted pelvis (all types)	240
Cephalopelvic disproportion	82
Placenta previa	33
Pre-eclamptic toxemia and nephritis	29
Previous cesarean section	32
Elderly primipara	21
Previous extensive plastic repair	16
Pelvic tumor (fibroids)	12
Pelvic tumor (ovarian cyst)	1
Cardiac disease	7
Diabetes	8
Unengaged breech	8
Large baby	5
Cervical dystocia	6
Transverse presentation	4
Rupture of uterus	3
Elective	2
Previous myomectomy	2
Premature separation of placenta	3
Twins (previous section)	2
No engagement (vertex)	2
Mental depression	2
Fetal distress	2
Threatened rupture of uterus	1
Pulmonary tuberculosis	1
Previous complete laceration (2)	1
Osteoarthritis	1
Previous section, sterilization, implantation of tubes	1
Torsion of uterus	1
Midplane arrest	1
Prolonged labor	1
Face presentation	1
Brain tumor	1
Sacroiliac injury	1
Psychopathic fear of labor	1
Carcinoma of rectum	1
Congenital dislocation of hips (arthroplasty)	1
Total	536

The success of cesarean section has carried with it an inordinate broadening of the indications, so that many physicians feel that it is too frequently performed.

In 1918, the indications were very few; approximately 95 per cent were performed for some type of contracted pelvis. Since then, additional indications include almost every possible complication to which pregnant women are subject. Also, at that time, it was difficult to persuade the patient and her family to permit a necessary cesarean section. Today, if the labor seems too prolonged, the family and relatives ask why cesarean is not being considered or done. If the child should die by delivery *per vias naturales*, the implication in some instances is that the case has been mismanaged, that the physician should have known enough to do a cesarean section in the first place, and that if some other doctor (sometimes mentioned by name) had had the case he would have done a cesarean. I have encountered acquiescence to this at-

titude in certain members of the profession. What has brought it about? No doubt the many reports of large series of cases with almost no mortality and the failure to study the reports properly. Also, I doubt that all men publish all their poor results, since we have been able to find so many casualties in the reports of the Maternal Mortality Committee of New York City.

What are the indications for doing a cesarean section? The absolute indications for cesarean section are few. The main one is the presence of pelvic deformity or contraction of such degree that the birth of a living child is absolutely impossible. Almost all other indications must be considered as relative, since it would be possible to deliver the fetus through the birth canal, though at the risk of a terrific sacrifice in fetal life and resultant damage and subsequent permanent invalidism to the mother.

What can we consider as relative indications? The most common is relative disproportion between the size of the fetus and the pelvic capacity. The severe degrees of contraction are easily recognized. The minor ones, the borderline types constituting the largest group, are more common and the ones with which we have to deal most frequently. The management of the borderline pelvic indications for cesarean continues to be a problem. There is always great danger in delaying the operation until there is exhaustion in the mother, which may lead to infection and other complications, perhaps even to the death of the child, irrespective of the type of delivery. In our series, there were 240 cases of contracted pelves of all types (44.77 per cent) and 82 cases of cephalopelvic disproportion (15.29 per cent), making a total of 322 cases. Of this number, 125 (38.82 per cent) had had x-ray and pelvimetry before operation.

Where real doubt exists, x-ray studies should be made early in labor, and interpretation should be made by both the obstetrician and the roentgenologist; otherwise, the report loses much of its value. The roentgenologist sees only one side of the picture and is not able to give a full, satisfactory report; he does not take into consideration the molding of the head, nor does he know the physical setup or make-up of the patient. Several of our babies were delivered through borderline pelves when the x-ray had reported a definite disproportion.

We often hear the question, "Shall we allow a test of labor?" What constitutes a test of labor? No two definitions are alike. I quite agree with Waters when he states that a "test of labor" depends upon the character, frequency, and effectiveness of first stage uterine contractions and correlated factors, such as physical status and emotional balance of the patient.² In our series, we found that the incidence of sections increased when there was a trial or test of labor and x-ray studies.

Previous operations, including cesareans, are also relative indications. In our series, 16 cases had had extensive vaginal plastic operations for partial prolapse, complete lacerations of the perineum, and rectovaginal fistula. Previous sections had been done in 143 cases. There were 107 with one previous section, 29 with two previous sections, four with three previous sections, one with four previous sections, and two with five.

Previous cesarean occurred as a major indication thirty-two times. Its indication is not always valid, for much depends on the type previously performed, the postoperative course, and whether it was done for an absolute or a relative indication. Previously sectioned patients bring up the question of whether we should subscribe to the doctrine of "once a section, always a section." I have in a few instances successfully delivered patients through

the pelvis who had had previous section for only relative indications. But one never knows how strong the uterine scar is, so that no matter how uneventful the convalescence may have been, I believe that it is not wise to wait and wonder if and when the uterus may rupture. Even though a patient has had pelvic deliveries after a section, it does not necessarily follow that she will go through another pregnancy safely. In most cases of a previous classical section, if the scar is thin, we do a repeat section about a week before the estimated date of confinement. Most of the reported ruptures have been through classical scars. According to Kerr³ and Audebert⁴ the percentage varies from 4 to 6 per cent. The generally accepted figure seems to be 4 per cent. Gepfert⁵ reported a case of antepartum rupture of the uterine scar following low-flap cesarean section. With the potential rupture always in mind, it would seem that the best interests of the patient are served if she is carefully watched; and unless the head is well down and the cervix well attenuated, a cesarean should be done.

Other relative indications are the presence of fibroids and breech presentations. In twelve cases, cesareans were done because of fibroids. These were cases in which the fibroid was low down in front of the head, preventing its coming into the pelvis. Fibroids in other locations are no indication for cesarean. Eight cesareans were done for breech presentations. These were cases of early rupture of the membranes, short labor, closed cervix, and a large baby. Breech presentation per se is not an indication for section; instead, we should try to determine the true cause for the indication, whether it be a fetopelvic disproportion or some other complicating factor.

TABLE III. OBSTETRIC HISTORY OF PATIENTS

	NO. OF CASES	MATERNAL DEATHS		INFANT DEATHS		STILLBIRTHS		TOTAL FETAL MORTALITY	
		NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
Total	536	10	1.86	27	5.04	25	4.66	52	9.70
Primiparas	311	6	1.92	16	5.14	16	5.14	32	1.028
Multiparas	225	4	1.77	11	4.88	8	3.56	19	8.44
<i>Previous Sections:</i>	143	2	1.39	5	3.49	0	0.00	5	3.49
One previous section	107	1	0.93	7	6.54	0	0.00	7	6.54
Two previous sections	29	1	3.44	1	3.44	0	0.00	1	3.44
Three previous sections	4	0	0.00	0	0.00	0	0.00	0	0.00
Four previous sections	1	0	0.00	0	0.00	0	0.00	0	0.00
Five previous sections	2	0	0.00	0	0.00	0	0.00	0	0.00

Table III gives a résumé of the obstetric history of the patients. The mortality rate of 1.86 compares favorably with the general mortality rate of 2.51. The majority of these cases had elective cesarean section without trial labor. Two of the deaths occurred in patients who had had previous sections (one having had one, and the other having had two).

One hundred eleven of these cases had had previous vaginal delivery. Two of these mothers died following cesarean. There were twenty-four stillbirths and seven babies dying following delivery, a total fetal mortality of 31, or 8.52 per cent. Included in the number of stillbirths in these one hundred eleven cases were two sets of premature macerated twins and four full-term macerated babies.

Table IV gives the ages of patients. The most favorable age group seemed to be that in the twenties. In the small group of patients 38 years of age and over, the maternal mortality rate, as well as the fetal mortality rate, was more than doubled. This study would indicate that the risk to both mother and baby is markedly increased as the mother reaches the fortieth year group.

TABLE IV. AGE OF PATIENTS

	ALL CASES			PRIMIPARAS			MULTIPARAS		
	NO. OF CASES	MATERNAL DEATHS		NO. OF CASES	MATERNAL DEATHS		NO. OF CASES	MATERNAL DEATHS	
		NO.	RATE		NO.	RATE		NO.	RATE
All ages	536	10	1.86	311	6	1.93	225	4	1.77
13 to 19 years	14	0	0.00	13	0	0.00	1	0	0.00
20 to 24 years	83	0	0.00	61	0	0.00	22	0	0.00
25 to 29 years	129	2	1.55	76	1	1.31	53	1	1.88
30 to 34 years	135	3	2.22	68	2	2.94	67	1	1.46
35 to 39 years	120	4	3.33	61	3	4.91	59	1	1.69
40 to 46 years	54	1	1.85	32	0	0.00	22	1	4.52
47 years	1	0	0.00	0	0	0.00	1	0	0.00

CONDITION OF THE MEMBRANES
IN 536 CESAREAN SECTIONS

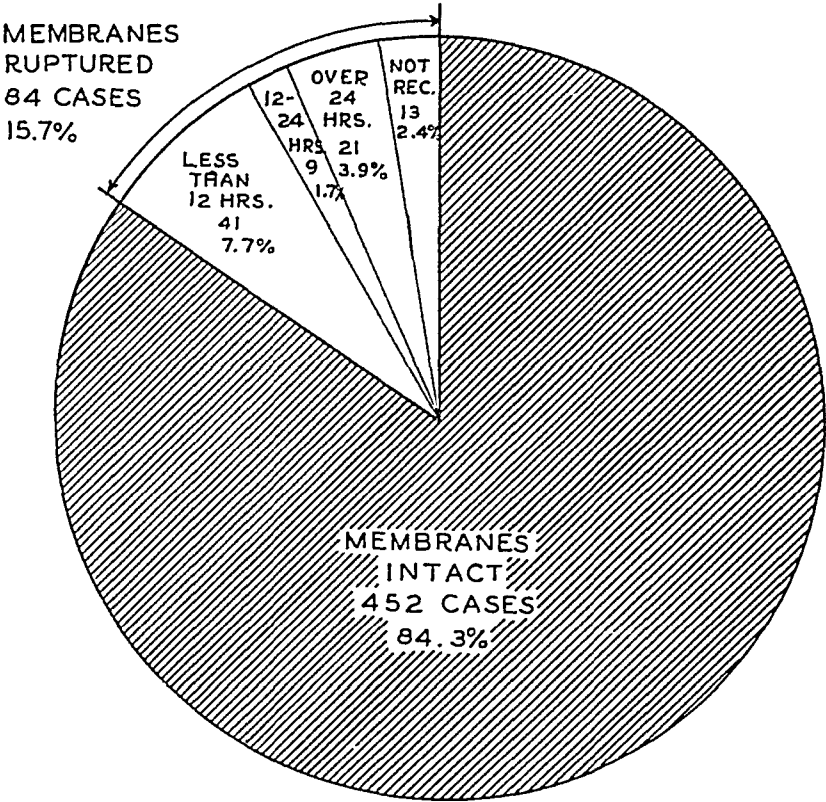


Fig. 2.

Table V shows the condition of the membranes. In women with intact membranes at the time of operation the maternal death rate is usually lower than in those in whom the membranes are ruptured. In contrast to this, our series showed the death rate was higher in the cases with intact membranes, nine cases, or 1.99 per cent.

TABLE V. CONDITION OF THE MEMBRANES

	NUMBER OF CASES	MORBIDITY		MORTALITY	
		NO.	RATE	NO.	RATE
All cases	536	66	1.23	10	1.86
Membranes intact	452	47	1.40	9	1.99
Membranes ruptured less than 12 hours	41	8	1.95	0	0.00
Membranes ruptured 12 to 24 hours	9	1	1.11	0	0.00
Membranes ruptured 24 hours and over	21	8	3.80	0	0.00
Time of rupture not recorded	13	2	1.54	1	0.77

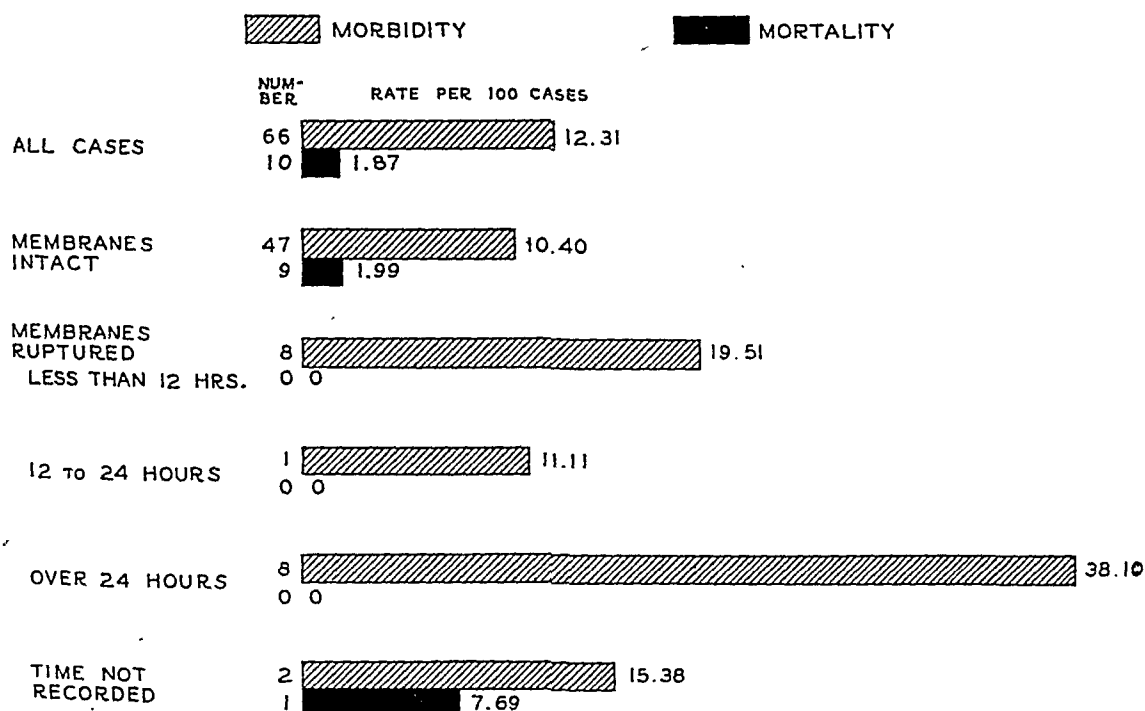
MATERNAL MORBIDITY AND MORTALITY
BY CONDITION OF MEMBRANES

Fig. 3.

Table VI summarizes the maternal and fetal mortality in relation to the duration of labor before cesarean section was performed. It has long been recognized that the death rate is higher in those women having cesarean section the longer they have been in labor than it is in those sectioned prior to the onset of labor.

TABLE VI. DURATION OF LABOR

	NO. OF CASES	MATERNAL DEATHS		INFANT DEATHS		STILLBIRTHS		TOTAL FETAL MORTALITY	
		NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
All cases	536	10	1.86	27	5.04	25	4.66	52	9.70
No labor	356	4	1.12	20	5.62	12	3.37	32	8.99
Less than 6 hours	30	1	3.33	0	0.00	3	10.00	3	10.00
6 to 12 hours inclusive	54	4	7.4	3	5.55	2	3.70	5	9.25
13 to 24 hours inclusive	51	1	1.96	2	3.92	5	9.80	7	13.72
Over 24 hours*	44	0	0.00	2	4.54	3	6.81	5	11.36
Time not recorded	1	0	0.00	0	0.00	0	0.00	0	0.00

*Longest time of labor recorded was 84 hours. There were eight cases ranging from 62 to 84 hours.

Four of these maternal deaths occurred without labor, in patients with serious prenatal complications, such as pulmonary tuberculosis, severe grade of cardiac disease, toxemia, and brain tumor. If we were to omit these cases having severe prenatal complications, the elective group would show a low death rate, 1.1 per cent. In the group having section after from six to twenty-four hours of labor, there was a rise in maternal mortality. It is interesting to note, however, that there were no maternal deaths in the forty-five cases who had twenty-four hours or more of labor.

Table VII details the anesthesia used. Nearly all the cesarean sections were done with inhalation anesthesia, usually cyclopropane combinations, or gas-oxygen-ether combinations. There were only three cases of spinal anesthesia. Gas-oxygen-ether had the highest maternal mortality. Local anesthesia with inhalants was used in 13 cases.

TABLE VII. ANESTHESIA

	NO. OF CASES	MATERNAL DEATHS	
		NO.	RATE
Total	536	10	1.86
Cyclopropane-oxygen	189	1	0.53
Cyclopropane-oxygen-ether	165	0	0.00
Gas-oxygen-ether	162	8	4.94
Local with inhalants	13	1	7.69
Ether	3	0	0.00
Spinal	3	0	0.00
Gas-oxygen-ethylene	1	0	0.00

Choice of Type of Operation

Each operation has its place. The classical operation is the oldest and now the least often performed. It was the operation chosen by the occasional operator because it has always been the easiest to perform; yet, of all types of cesareans, it no doubt carries the highest percentage of postoperative deaths.

In our series, the pendulum has swung markedly from the classical to the low segment transperitoneal operation. We found the low segment operation the best for clean cases and the low transverse cervical incision the technique most suitable. The results shown indicate its superiority over the old classical and the reasons why it has so rapidly come to the front. Its use is one of the greatest single factors in reducing mortality in cesarean section. Also, another great advantage of the low segment operation lies in the fact that, because it is easy to demonstrate the anatomy and have full vision of the field at all times, this method can, without difficulty, be taught the members of the resident staff.

Fig. 4 shows the increase of the low cesarean section over the classical during the last seven-year period in our series. In many clinics, classical cesarean carries approximately a 5 per cent mortality; whereas the lower segment operation has only 1 or 2 per cent. That, of course, is another reason why the latter technique is rapidly replacing the classical. The classical operation is reserved for the elective case, i.e., the woman not in labor. It is very useful when speed is essential, as in cases of accidental hemorrhage with almost no dilatation and with mother and baby in danger. It may be the easiest operation in a cardiac case or the choice in a clean case of placenta previa.

Heretofore, the other types of operation were used in potentially infected cases; nowadays they are also done in the clean and elective cases. Thus the low flap is done in all cases, in early or late labor, with little or no contamination.

It is difficult to understand how, on the one hand, vein valve spasm can be sufficient to cause distention, followed by thrombosis and necrosis of the villi, thereby causing hemorrhage, abruptio, and toxemia, and, on the other hand, that fetal death leaves the placenta intact and without necrosis because the intervillous maternal circulation is sufficient to keep the villi alive.

Dieckmann believes that the primary pathology of abruptio lies in the maternal vessels of the compact muscle layers of the uterus. Hertig holds that necrosis of the decidua results from acute degeneration of the precapillary arterioles of the placental site. Occasionally toxemia is found with a hydatid mole which has no fetal vessels to thrombose and produce infarcts. Such reports, plus the spread of the hemorrhage through the middle and outer layers of the uterus and the subserosa of other pelvic structures in the Couvelaire type of abruptio placentae, would seem to place the primary pathology on the maternal rather than on the fetal side of the placenta.

More work must be done to clear up these different points of view. Unfortunately, toxemia still remains a "disease of theories."

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—It has been some time since I have had the privilege of discussing a presentation by Dr. Bartholomew on placental pathology. I find much to my amazement that after these several years we are still diametrically opposed in our ideas as to the etiology of placental necrosis and its relationship to eclampsia.

Many of the thoughts that I have had in mind as I have listened to this paper have already been expressed by Dr. Reis but some of them may be emphasized again. The crux of this question which has been raised by the author depends upon whether these lesions of the placenta arise on the fetal side or on the maternal side of the placenta, and whether they precede or follow the toxic manifestations which Dr. Bartholomew has described.

Dr. Bartholomew would have us believe that there are several conditions in the fetal circulation which may be productive of infarction and necrosis of the placenta, and secondary toxemia in the mother. There are many indications to point out that death of the placental villi or life of the placental villi is not dependent upon circulation on the fetal side of the placenta. Prominently among these conditions he has mentioned thrombosis or obliteration of the fetal placental vessels.

However, there are many circumstances which point to the fact that the fetal villi and the chorionic epithelium receive this nourishment from the maternal circulation and are very little dependent on the fetal circulation for their vitality. For instance, after the death in utero of a fetus from some such cause as congenital syphilis, one frequently finds the chorionic epithelium and the villi quite well preserved for 3 or 4 weeks after the fetus has died and all fetal circulation, therefore, has been cut off. However, after premature separation of the placenta, one finds the villi adjacent to the retroplacental clot promptly and immediately degenerated as soon as they are cut off from the oxygen supply in the mother's blood. Also, the findings of hydatidiform mole, as have been mentioned by Dr. Reis, are indicative of the fact that chorionic epithelium is not dependent upon a fetal circulation for its vitality for in this case the chorionic epithelium flourishes, the villi grow rapidly; and yet there is no fetal heart or no fetal circulation to supply these villi with blood from within the villous core.

One may find all of the vessel lesions which Dr. Bartholomew has described at the margin of any normal placenta, where the villi and the villous vessels and fetal vessels have undergone degeneration at their site of attachment to the poorly nourished decidua reflexa.

There are doubtless several mechanisms for the formation of a placental infarct, and certainly one of the most common ones is the formation of an intervillous thrombosis of a local portion of the maternal lake of blood. These recent intervillous thrombi contain red blood cells and are red and firm in consistency. When the red blood cells have undergone autolysis and absorption, a fibrinous mass is left which is gray and firm in consistency. With the first formation of this thrombosis, the villi are cut off from their contact with the oxygen

it is a safe procedure. After delivery, whether from above or below, the uterus should be packed.

It is generally agreed that cesarean section is the method of choice in cases of placenta previa in the primipara; and also generally in cases of placenta previa when the cervix is undilated, when the fetus is at term, alive and viable, when there has been no vaginal interference, and when manipulation from below would be dangerous. The low cervical cesarean is the best type of operation for complete placenta previa, for other types presenting a closed cervix, and for the incomplete varieties of placenta previa when the cervix is long and undilated.

In our series, we had 33 cases (6.1 per cent) of placenta previa, with one death, which we charted as a preventable death, occurring in a para iii who had had two previous sections and who entered the hospital seven hours after the onset of bleeding.

Cases of partial separation of the placenta should be individualized, for the pathology varies from almost nothing to the very dangerous type known as uteroplacental apoplexy. In cases of partial separation in which there is only moderate hemorrhage and the fetus is viable, the decision of whether to do a cesarean section or to deliver from below is a difficult one. Mild forms of separation respond well to the usual therapy, especially in a multipara with a dilated and well-effaced cervix, a fetus of normal size, and a pelvis not too contracted. If the patient is in labor she will require careful observation; if the separation is accompanied by progressive symptoms of blood loss and shock, irregularity of the fetal heart, colicky pains, hard uterus, a cervix long and closed or rigid, a section should be done at once with plenty of blood replacement and shock therapy.

TABLE VIII. CAUSES OF POSTPARTUM MORBIDITY

Postpartum morbidity, all causes	66
Sapremia	21
Infected abdominal wound	13
Pyelitis	5
Pyelonephritis	2
Pneumonia	2
Phlebitis	2
Shock	2
Hematoma of wound	2
Bronchitis	2
Mastitis	1
Tonsillitis	1
Septicemia	1
Parotitis (bilateral)	1
Peritonitis (general)	1
Cystitis	1
Atelectasis	1
Salpingitis	1
Hemorrhage	1
Postpartum convulsions	1
Thrombophlebitis	1
Secondary anemia	1
Coryza and pharyngitis	1
Heart conditions	1
Suture of packing to uterus	1
Total	66 Rate 12.3%

In every cesarean section there is danger of hemorrhage, from the time the incision is made into the uterus until after the patient's return to her bed. The control of hemorrhage during operation upon a normal uterus would

In our series, the Waters and Latzko operations, which have the advantage of allowing drainage, were done in the cases long in labor, potentially contaminated. There were sixteen such cases, among them eight which ranged from sixty-two to eighty-four hours in labor and in which both mothers and babies were saved.

The Porro operation is the choice for the badly contaminated case with a noncontractile, grossly infected uterus and for cases of Couvelaire uterus. In our series, it was done for nonremovable tumors in eight cases.

TYPE OF CESAREAN SECTION PERFORMED

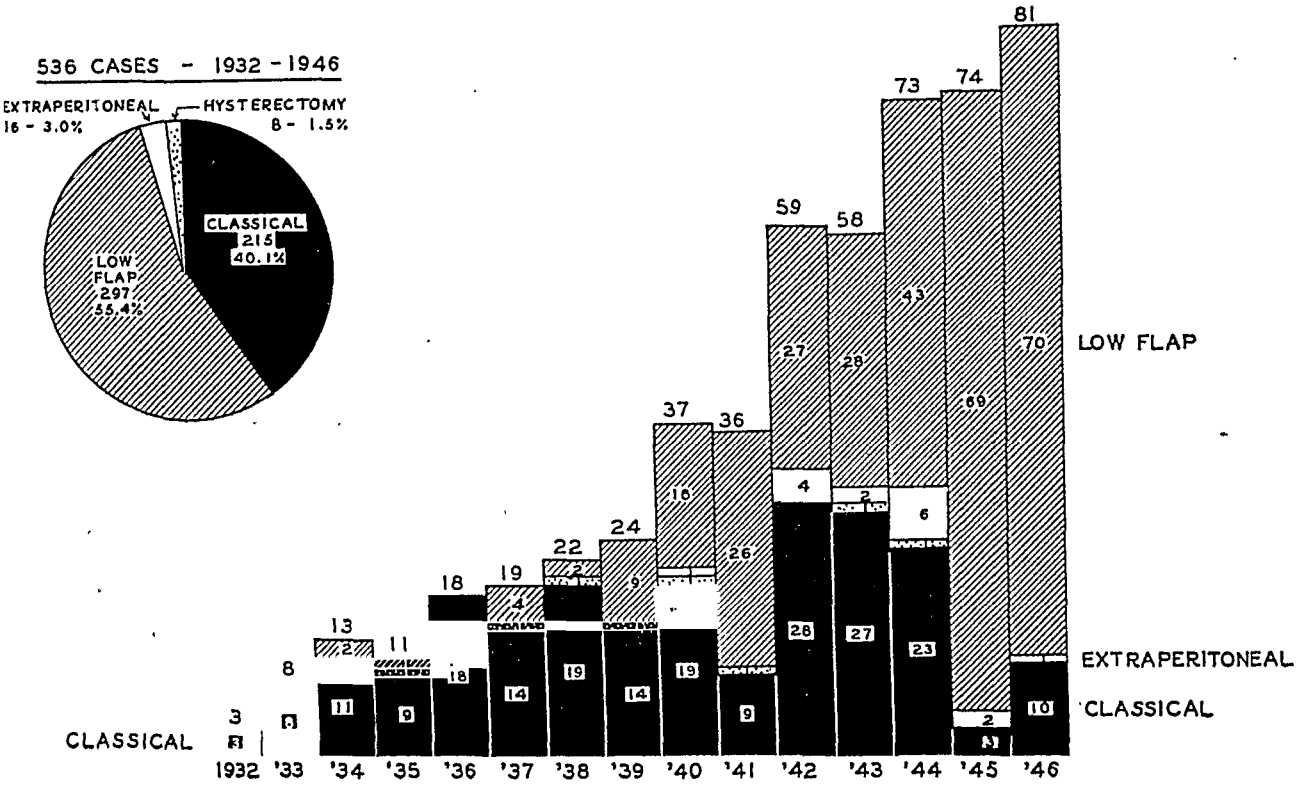


Fig. 4.

Hemorrhage

In the antepartum period, we have to deal with two conditions: placenta previa, and partial separation of a normally implanted placenta.

A placenta removed from the lower uterine segment before it is dilated and attenuated by the passing child is not, as experience has shown, attended by serious hemorrhage; but the detachment of a placenta previa, following (or preceding) the delivery of a child *per vias naturales*, is always attended with great loss of blood, and many of these patients have died of postpartum hemorrhage for lack of sufficient contraction in the overstretched lower segment of the uterus.

In the treatment of placenta previa, cesarean section has come into greater prominence since Bill,⁶ in 1927, reported the results of prophylactic blood transfusions and section. The Voorhees bag is sometimes mentioned; but unless one is experienced in the inserting of the bag, there is danger of increasing the separation and prolonging the labor. A few parous patients with a well-dilated, effaced cervix have been delivered safely vaginally. If the bag can be inserted without difficulty in the well-selected case, I feel that

Analysis of Maternal Deaths

In analyzing the ten deaths, we find that four of the patients died from causes complicating pregnancy and labor or from other systemic conditions, and that the method of delivery could not have been a factor in the cause of death. Six of the deaths occurred in the first six years of the service, after which there was one a year for the next four years. There were no deaths following cesarean section in the years 1937, 1938, 1940, 1941, 1944, 1945, and 1946.

TABLE X
MATERNAL MORTALITY

YEAR	AGE	PARA	STAT.	WEEKS PREG	PAST HISTORY	ANTEPARTUM & INTRAPARTUM HISTORY	HOURS OF LABOR	POSTPARTUM HISTORY	CAUSE	BABY	REMARKS
1933	38	I	P	38	NEGATIVE	NEPHRITIC TOXEMIA	0	AFTER 8½ HRS.	SHOCK	LIVING (4 LB. 7½ OZ.)	— NON- PREV.
1933	32	II	P	39	PULMONARY TBC PREV. SECTION	PULMONARY TBC. ARR PREV. SECTION	0	IN 24 HRS	SHOCK	LIVING (7 LB. 9 OZ.)	— NON- PREV.
1934	26	I	P	38	NEGATIVE	GEN CONTR PELVIS	9	ON 4TH DAY	AC. INTEST. OBST. PERITONITIS	LIVING (6 LB. 6 OZ.)	COLOSTOMY —
1935	34	I	P	32	RHEUMATIC HEART DISEASE	CLASS II CARDIAC	0	AFTER 15 HRS.	CARDIO- VASCULAR COLLAPSE	EXPIRED IN 14 HRS. (2 LB. 9 OZ.)	— NON- PREV.
1935	32	I	P	38	NEGATIVE	GEN. CONTR PELVIS ANDROID	8½	ON 7TH DAY	PERITONITIS	LIVING (6 LB. 1 OZ.)	AC. ENDOCARDITIS AC. PERITONITIS + NON- PREV.
1935	39	I	P	40	NEGATIVE	CONTR PELVIS C. P. D.	4	IN 7 HRS.	HEMORRHAGE	LIVING (8 LB. 10 OZ.)	SEPARATION OF UTERINE WOUND + PREV.
1936	37	I	W	40	NEGATIVE	LARGE BREECH	24	ON OPER. TABLE	HEMORRHAGE	LIVING (9 LB. 10 OZ.)	SEPARATION OF UTERINE WOUND + PREV.
C 1939	37	VI	P	42	1ST ECLAMPSIA 3 DIFF. INST DEL.	C. P. D. FAILURE TO ENGAGE	6	ON 4TH DAY	PERITONITIS	LIVING (8 LB. 10 OZ.)	— NON- PREV.
1942	43	III	P	36	2 PREV. SECTIONS	PLACENTA PREVIA COMPLETE	8½	ON OPER. TABLE	HEMORRHAGE	EXPIRED IN 1½ HR. (6 LB. 11 OZ.)	ADMITTED TO HOSP. 7 HRS. AFTER ONSET OF BLEEDING PREV.
D 1943	28	III	P	32	2 VAG. DEL. 1 MISCARRIAGE	BRAIN TUMOR	0	IN 32 HRS	GLIOMA	TWIN LIVED 2 HRS. (PREM.)	GLIOMA OF LEFT LOBE + NON- PREV.

NOTE: ALL CLASSICAL CESAREAN SECTIONS.
G-O-E ANESTHESIA EXCEPT FOR (C)
CYCLOPROPANE AND (D) LOCAL.

NOTE: + INDICATES POSTMORTEM.
UNLESS SO NOTED THERE
WAS NO POSTMORTEM.

As the incidence of cesarean section markedly increased, there was a decrease in the maternal death rate. This decrease no doubt was brought about because of the holding of early consultations, the performing of cesarean sections earlier in labor, and the avoiding of prolonged labor with its various complications, among them maternal exhaustion and ruptured membranes.

Some of the deaths, those from hemorrhage, could have been prevented had we had then, as we have today, the improved operative technique, the adequate preoperative replacement of the blood lost, and the control of hemorrhagic shock. Today, thanks to a well-functioning blood bank for which donors are always available, we are able to give transfusions to patients whose hemoglobin and red blood counts are low. In our cases of hemorrhage, placenta previa, and premature separation of the placenta, blood is given before, during, and after the operation, if necessary.

seem to be a simple problem; yet, three women died after classical sections, two on the operating table, and one in bed seven hours following the section. The two deaths on the table were from separation of the suture line and hemorrhage, as confirmed by autopsy.

Still we have come a long way since 1905, when Dr. Rudolph Holmes⁷ summed up the mortality in cesarean section by stating that cesarean section lowered infant mortality 30 per cent, but increased maternal mortality nearly threefold. Today, with our improved operative technique, adequate pre-operative replacement of the blood lost, the control of hemorrhagic shock, cesarean section appears to be three times safer for the mother than is the expectant obstetrical treatment; this safety also holds true for the baby.

Table VIII lists the major causes of postpartum morbidity. The accepted morbidity standard in this series has been that any woman showing a temperature of 100.4° F. on any two successive days after the first forty-eight hours is considered morbid from childbirth. All wound complications, serious or otherwise, were included. Sepsis was our main cause of morbidity, 31.8 per cent; the next was wound complications of all kinds, 19.7 per cent.

TABLE IX

CAUSES OF FETAL MORTALITY

IN 215 CLASSICAL CESAREANS

STILLBIRTHS _____	9	NEONATAL DEATHS _____	14
ABRUPTIO PLACENTAE _____	3	PREMATURITY _____	5
UNEXPLAINED _____	2	UNEXPLAINED _____	4
CARDIO-VASCULAR DISEASE (MAC.) _____	1	ATELECTASIS (PM.) _____	2
DIABETES (MAC.) _____	1	CONGENITAL HEART _____	1
TORSION OF UTERUS _____	1	LOBAR PNEUMONIA _____	1
CONGENITAL HEART (PM.) _____	1	HEMORRHAGE _____	1

IN 297 LOW FLAP CESAREANS

STILLBIRTHS _____	14	NEONATAL DEATHS _____	13
LARGE BABIES (2)		ATELECTASIS (PM.) _____	4
(1) 11 LB. 12 OZ. (MAC), UNEXPLAINED _____	1	HEMORRHAGE IN MEDULLA (PM.) _____	2
(2) 10 LB. 3 OZ., 24 HOUR LABOR _____	1	PREMATURITY _____	2
MACERATED _____	3	TOXEMIA _____	1
TWINS _____	3	RUPTURE OF LUNG _____	1
ASPHYXIA _____	2	HYDROCEPHALUS _____	1
ABRUPTIO PLACENTAE _____	1	MEGALOCEPHALIC _____	1
PREMATURITY _____	1	CONGENITAL ATRESIA OF SMALL	
UNEXPLAINED _____	1	INTESTINE (PM.) _____	1
ERYTHROBLASTOSIS _____	1		

IN 8 HYSTERECTOMIES

STILLBIRTHS _____	2
RUPTURE OF UTERUS (FETUS IN ABDOMEN) MACERATED _____	1
RUPTURE OF UTERUS, PLACENTA ACCRETA, FIBROIDS _____	1

NOTE: THERE WERE NO STILLBIRTHS OR NEONATAL DEATHS FOLLOWING 16 EXTRAPERITONEAL SECTIONS.

Table IX shows the incidence of stillbirths found in classical cesarean section, 4.18 per cent; in low cervical section, 4.71 per cent. In the Porro group, the stillbirths were 25 per cent. There were no stillbirths and no neonatal deaths in extraperitoneal sections. The total fetal mortality in classical cesareans was 10.69 per cent. The total fetal mortality in low cervical sections was 9.99 per cent.

Discussion

DR. PAUL TITUS, Pittsburgh, Pa.—Dr. Hennessy's series is from one hospital but from a group of 32 different operators, of whom 25 were members of the hospital staff, but perhaps not all in the Department of Obstetrics, while seven were courtesy staff members. How closely their indications and decisions could be supervised and controlled, and their varying operative ability supported by proper assistance is difficult to judge.

The general mortality rate following cesarean is still much higher than necessary throughout the country. It can and must be improved. While this risk continues, with some abatement but still with more hazard than there should be, the indications for cesarean have been greatly broadened and its incidence greatly increased.

Hennessy has some interesting figures bearing on this subject. In 1932, for example, their incidence was one cesarean in forty deliveries; by 1946 the rate had become one in twenty-four. He cites their total death rate for the fifteen years as 1.8 per cent. Seven of these deaths were in the first 5 years, 2 in the second, and only 1 in the third five-year period. He did not point out the creditable fact that 345, or more than half of their total cesarean sections were done in the third five years, so that their record for results has shown an even more striking improvement than appears at first glance.

In our smaller clinic but with a closely knit divisional staff group, we have shown the same tendency toward less rigid indications and more cesarean sections. Hennessy's paper induced me to study our own figures and I find that our incidence of operation has become definitely too high. Our maternal death rate during the same fifteen-year period as Hennessy's report was 0.84 per cent, but even that low figure shows that the conditions for which cesareans are done and the operation are still a dangerous combination.

To show the changing trend, I recall in a paper in 1939 being quite critical of cesarean section for delivery of twins, on the ground that they are smaller and always less likely to show disproportion even with small maternal pelvises. I have now to admit, somewhat boastfully, to having done a cesarean section recently at Latrobe, Pa., for quadruplets. I hasten to add, however, that the patient had had a secondary trachelorrhaphy with scar tissue deposit, and was given a seven-hour trial labor before the operation.

We have a required consultation rule for all obstetric cases showing even minor complications. This is enforced and is definitely not "mere polite agreement." Operative privileges are restricted, and both consultations and operations are supplied without charge to these patients of our courtesy staff or restricted medical patrons of our Hospital.

These men have found this an agreeable "postgraduate course" in obstetric complications, applied to their own practices, and do not, nor could they, take exception to the regulations.

By long custom, it never even occurs to members of our general hospital staff, holding surgical privileges, to undertake a cesarean section. They do general surgery better than we do; do obstetric surgery better than they; we all agree and adhere to this and that is the end of the matter, by unwritten and friendly agreement and cooperation. Why this cannot be so in all hospitals I cannot understand, and I might add in passing that this same staff arrangement holds with us for gynecology also. Nevertheless, with all these restrictions, our increasing incidence of sections has made it necessary for us to establish as a routine part of the weekly formal rounds a detailed review of every cesarean section case.

Several other outstanding points in Dr. Hennessy's paper should be referred to for special note because of their interest.

He emphasizes x-ray of the pelvis before or during labor, especially when disproportion is apparent. He appreciates that borderline pelvises are one's greatest problem. His three main indications for cesarean section are contracted pelvis (44 per cent), cephalopelvic disproportion (15 per cent), and placenta previa (6+ per cent).

He cites an unusually good record of no newborn or maternal deaths in sixteen extra-peritoneal cesarean sections, done for entirely valid reasons, including some instances of neglected or protracted labors.

Résumé

In considering the 536 cesarean sections done at St. Vincent's Hospital by numerous obstetricians during the past fifteen years, we have made a sharp distinction between the ward and private cases. By contrast and comparison of these two services, we are able to render a more detailed report. This series shows that in the 536 cases (158 ward and 378 private), the incidence was 1:57 in the ward cases as compared with 1:17 in the private cases. Thus we see that the old adage of safety in numbers still holds true.

The three main indications for cesarean were: contracted pelves, 240 cases (44.77 per cent); cephalopelvic disproportion, 82 cases (15.29 per cent); and placenta previa, 33 cases (6.15 per cent).

The type of operation preferred is the low segment transperitoneal which has the great advantage, among many others, of contributing markedly to the decrease in maternal deaths.

In the 536 cases of cesarean section, there were ten maternal deaths (1.86 per cent), constituting 22.72 per cent of the total obstetrical mortality. Deaths from hemorrhage, the chief cause of mortality, have been greatly lessened by means of an adequate preoperative replacement of the blood lost and the treatment of hemorrhagic shock.

From these findings, it is possible that our main faults in treatment have been the failure of securing early consultation, the finding of too many relative indications, the poor selection of the type of cesarean section, and the belated treatment of our hemorrhage cases. Nevertheless, with so many men operating, the final results are encouraging. Whenever there is only one man operating, he will get a low mortality for several hundred cases; whereas, in clinics in which there are many men operating, there is bound to be a higher mortality.

If we are to accomplish any improvement in the figures shown, a review of the errors in judgment, technique, and treatment must be undertaken from time to time and forcibly brought to the attention of the various operators. This is done at our hospital in the monthly conferences. The Maternal Mortality Committee of New York City, which at its monthly meetings carefully studies every maternal death, has also, through careful supervision and thorough analyses, been a great force in the improvement of our mortality rate.

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We concur with Dr. Hennessy's opinion that fewer sections are done on the indigent patients. On the other hand, we found both a higher maternal and fetal mortality in this group.

We found that the establishment of a city-wide ironclad rule that a free compulsory consultation by a certificated staff member would satisfactorily adjust our section problem.

Dr. Hennessy has intimated, and we have proved, that with the restriction of operators to only qualified obstetricians, and with the performance of the low segment operation, the maternal mortality can be reduced to a negligible factor.

Dr. Hennessy is to be congratulated on his excellent presentation of a very timely subject. I appreciate the amount of time and effort expended in preparing his paper.

DR. C. O. McCORMICK, Indianapolis, Ind.—The two entries of a cesarean section report that always attract our attention primarily, are the incidence of the operation and the maternal mortality. This is largely true because these two factors are the more or less generally accepted criteria used in judging the quality of obstetrics practiced in any given clinic.

Seeking a national mean of each of these two items, I have prepared a slide showing the respective figures, covering the five-year period 1941 to 1945, inclusive, gathered from twenty leading American clinics (Table I).

TABLE I. RECENT CESAREAN STATISTICS AS TO INCIDENCE AND MATERNAL MORTALITY
(TAKEN FROM TWENTY OF THE LEADING AMERICAN CLINICS)
1941 TO 1945 INCLUSIVE

CLINIC	TOTAL NUMBER OF DELIVERIES	CESAREAN SECTION			
		NUMBER	INCIDENCE PER CENT	MATERNAL DEATHS	MORTALITY PER CENT
Boston Lying-in	14,646	522	3.55	3	0.57
Chicago Lying-in	14,101	616	4.37	2	0.32
Cincinnati University	11,375	90	0.79	2	2.22
Cleveland Maternity	20,476	1,128	5.50	7	0.62
Duke University	5,648	105	1.85	1	0.95
Emory University	11,463	59	0.51	1	0.17
Georgetown University	8,408	192	2.28	0	0.00
Illinois University	3,275	118	3.60	3*	2.54
Iowa State University	5,045	103	2.04	0	0.00
Johns Hopkins	9,350	455	4.86	1	0.21
Los Angeles General	15,289	559	3.65	11	1.96
Margaret Hague	33,981	902	2.65	6	0.66
Mayo Clinic	3,967	145	3.65	0	0.00
New York Lying-In	16,351	535	3.27	2	0.37
Pennsylvania University	11,893	840	7.06	3	0.35
Providence Lying-in	23,662	746	3.15	2	0.26
Stanford University	6,836	429	6.26	0	0.00
Texas University	4,556	123	2.69	1	0.81
Tulane University	10,460	224	2.14	5	2.23
Washington Univ. (St. Louis)	13,587	227	1.67	0	0.00
Summary	244,369	8,118	3.32	50	0.61

*Two of these deaths followed antemortem sections.

It is noted that the average rate of incidence of cesarean section of these twenty clinics, reporting a total of 8,118 sections in a total of 244,369 deliveries, is 3.32 per cent; and that of maternal mortality, .61 per cent. From this we may deduce that leading American clinics do have creditably low rates of incidence of cesarean section and associated maternal mortality.

The corresponding figures, 3.44 per cent (1:29) and 1.86 per cent, given in Dr. Hennessy's report are favorably comparable, particularly since they represent a much longer period of study during the major part of which certain techniques and many modern forms of therapy were unknown.

He surprised me with a report from the literature of thirty-seven instances of uterine rupture following previous low flap cesareans (four of these before labor). He surprised me, also, with his own report of ten classic type cesareans in the eighty-one so recent as 1946.

The use of the Voorhees bag for any type of placenta previa is not even debatable, in my opinion.

Hennessy found the chief cause of cesarean deaths to be hemorrhage. In our clinic we have decreased the risk of this, as he has, by plasma and blood transfusions; also, by adopting Phaneuf's suggestion of the transverse incision in the lower uterine segment and by deliberate control of bleeding sinuses by a special clamp.

Hennessy's chief suggestions for lessening the death rate following cesarean sections are excellent. These are rigid though broadening indications and their control by competent consultation before any cesarean, assurance of competence in performance of the operation, and control of blood loss.

DR. ROLAND S. CRON, Milwaukee, Wis.—For many years we have been interested in the cesarean section problem, especially as it pertained to the County of Milwaukee as well as to the State of Wisconsin. At one time it appeared that the City of Milwaukee had one of the highest section rates of any large city in the nation. In one large private hospital the incidence ran as high as one in five deliveries.

A recent survey made of the performance at Milwaukee Hospital (private) and Milwaukee County Hospital (indigent and emergency) will be used as a comparison for the one presented by Dr. Hennessy. From the years 1933 through 1947, there were 19,883 deliveries at Milwaukee Hospital with 1,144 cesarean sections for an incidence of one in seventeen, or 5.7 per cent. Dividing this fifteen-year period into five-year intervals, the study shows that there was a 100 per cent increase in deliveries for each period but a very definite reduction in the incidence of sections from 7.4 per cent in the early period, to 5.5 per cent in the last one. Our most common indication for section has been a previous cesarean. We practice the dictum of once a cesarean always a cesarean. Our results prove the efficacy of that procedure. There have been no ruptured uteri and no deaths in the last 573 operations. Almost one-half, or 43.6 per cent, of this group were repeat sections. During the fifteen-year period there were ten deaths, giving a gross maternal mortality of 0.8 per cent.

We consider an incidence of 5 per cent to 5.5 per cent the irreducible minimum to which this operative treatment can be reduced. A rate lower than that we feel will produce a higher stillbirth and neonatal death rate, and there will result severe, and sometimes irreparable, damage to maternal soft parts.

The stillbirth rate was 2.1 per cent and neonatal deaths were 3.9 per cent.

The classical type of operation has been abandoned and the extraperitoneal found unnecessary.

Only certified obstetricians are now permitted to perform cesareans. There were twelve board members who did 560 of the last 573 sections performed.

The record at the Milwaukee County Hospital for 1943 to 1947 shows a much lower incidence of sections, namely, one in 48, or 2.5 per cent. Again, repeat sections were the most common indication. The low segment operation, with one exception, was the type of operation utilized. There was one death from bronchopneumonia. This series is a small one and is a good example of what happens in an industrial community where, during periods of high employment, medical and surgical care improves. During the previous five-year period there were 7,702 deliveries with 120, or 1.5 per cent, sections and eight deaths, or 6.6 per cent mortality.

In both institutions we have abandoned the use of caudal anesthesia because of two deaths and other complications attributed to that procedure. More and more we are relying upon Pentothal induction and gas for general anesthesia.

a more unnecessary rise in cesarean section incidence than the x-ray. The roentgenologist should be expected to give neither advice nor prognosis, but only his findings.

4. I find myself in agreement with the speaker in not being able wholly to endorse the dictum, "Once a cesarean, always a cesarean." However, this policy has been adopted by some of our larger clinics, and is finding favor with more and more operators.

Nevertheless, personal experience prompts me to be a little less radical. The late Dr. Stander of the New York Lying-In reported in 1944, 41 per cent of 360 previously sectioned cases in that institution as having been safely delivered from below.

In handling previously sectioned cases, two things should be kept ever in mind: (1) All such cases should be hospitalized. (2) Such a uterus should be allowed to withstand only the strain of pregnancy and the first stage of labor.

5. Dr. Hennessy's specified indications for the various types of section are for the most part well taken. While the classic operation may be the better choice in a few selected cardiac cases, it must be remembered that, as a group, cardiacs do not as a rule tolerate well section delivery, particularly the classic type. Also, in dealing with a placenta previa and an undilated cervix, I personally would not insist that the fetus be alive or at term. Better surgery dictates, "Molest a bleeding site the least possible."

6. It must be admitted that the usefulness of the extraperitoneal section even with its improved techniques is in general being much restricted by the success of the transperitoneal low segment operation, augmented by intravenous fluids, blood transfusion, antibiotics, sulfonamides, and abdominal decompression.

7. Dr. Hennessy's study brings forth the usual high gross fetal mortality of 10 per cent, which again reminds us that abdominal delivery cannot guarantee a living baby. Even normal-appearing babies breathing spontaneously not infrequently die a few hours after birth. Russ and Strong have demonstrated that direct tracheal aspiration of section-born babies produces 3 to 7 c.c. of mucoid material, and that of babies born per vaginam only 1 to 2 c.c. By adopting routine immediate intratracheal aspiration upon cesarean-born babies, they have reduced the death rate 80 per cent.

8. Two findings in Dr. Hennessy's study that run counter to general experience and customary teaching are the absence of maternal deaths in cases having more than twenty-four hours of labor and in cases having ruptured membranes.

DR. JOSEPH D. O'CONNOR, Worcester, Mass.—In regard to the incidence of section, Dr. Hennessy has stated that it is higher in private than in ward cases, a trend which is enhanced in no small measure by the anxiety hazard which confronts the obstetrician in cases where the element of friendship for the patient or her family inhibits the impersonal calm one may invoke with total strangers. It seems inevitable, therefore, that the incidence of section will be greater in hospitals where the census of private obstetrical admissions greatly exceeds that of the ward service. As a corollary to this thesis, the differences in the two types in physical and in nervous stamina undoubtedly play an important role in the incidence of the operation. The ability of the lethargic, rugged ward type of patient to endure the pain and effort of labor better than the educated, highly emotional, and frail private patient is well recognized.

Any attempt to elaborate on the excellent discussion by my predecessors on the indications for cesarean sections would be to "paint the lily." One finds it difficult, however, to refrain from observing that the number of indications for the operation is now legion, a condition probably begotten, in great measure, by an unwarranted fear of a stillbirth and the greater ease and safety of our present techniques of operation. Putting the brakes on this trend is no easy matter. Better teaching and training in the use of forceps at the higher pelvic levels are needed, and a better appreciation of the fact that cesarean section is not a panacea for all the problems of delivery.

The choice of operation still seems to be a moot question. While the classical operation has waned greatly in popularity, recent reported series of sections indicate that it is still too frequently invoked. It is much more deadly and a more frequent cause of morbidity than

When we analyze his data of the same five-year period, 1941 to 1945, inclusive (Table II), we observe that while his incidence of the operation (4.22 per cent) is fully 25 per cent higher than that of the twenty clinics (3.32 per cent), his mortality rate (0.33 per cent) is approximately but half that of the clinics (0.61 per cent).

TABLE II. INCIDENCE AND MATERNAL MORTALITY OF CESAREAN SECTION
ST. VINCENT'S HOSPITAL, 1941 TO 1945, INCLUSIVE

YEAR	DELIVERIES	SECTIONS	INCIDENCE	MATERNAL MORTALITY
1941	1000	36	-	0
1942	1251	59	-	1 (Placenta previa—preventable)
1943	1845	58	-	1 (Brain tumor—non-preventable)
1944	1647	73	-	0
1945	1365	74	-	0
	7108	300	4.22%	2—0.33%
Respective figures of 20 of the leading clinics 1941-1945			3.32%	0.61%

Many pertinent points arise in Dr. Hennessy's report. I will comment upon but a few of them.

1. Dr. Hennessy rightly stresses the growing importance of cesarean section in obstetric surgery. The incidence in his series doubled within fifteen years. While originally there was but one indication, fetopelvic disproportion, today that number has grown to approximately forty. Although the indications have greatly increased, the maternal mortality has decreased.

2. Relative incidence of cesarean section in private and ward patients. I am sure every staffman is aware that a definite disrelation on this basis exists in his clinic. Yet, I wonder if he knows just how great the discrepancy really is. Dr. Hennessy reports that in his clinic the incidence of the operation among private cases is more than three times that among ward cases—one in seventeen cases among the private, and one in fifty-seven cases among the ward patients—or 5.82 per cent against 1.75 per cent. In checking these two groups over the seven-year period, 1941 to 1947, inclusive, at our clinic at the Indiana University Medical Center, I was a little surprised to learn that we, too, had a ratio of over 3 to 1 (8.80 per cent : 2.80 per cent).

Personally, I question if such a discrepancy, and it no doubt exists more or less in all clinics, can be truly justified. Of course, there are bona fide factors that support to considerable extent this high disparity of over three to one. On the one hand, we have more elderly primiparas, more complicating disease because of greater age, a greater premium on fetal life, and so on; while, on the other hand, we are more often assisted by the ally youth, the importance of impressing upon students the value of conservative obstetrics, extending to students and the intern staff the privilege of observing protracted labor, et cetera.

Yet, the degree of discrepancy, which is sufficiently great to suggest discrimination, leaves much to explain away. The embarrassment, if any, is not lessened when we realize the greater frequency of repeat sections performed among private than among public or ward patients. Irving reports that at the Boston Lying-in, the ratio is more than two to one. During the past five years, the ratio at our clinic has been a little over one and one-half to one (0.71 per cent to 0.46 per cent).

Suffice it to say, "polite" consultations should be eliminated from the private group, and more "anxiety" applied to the ward group. In dealing with the ward patient, let us give her the advantage of early consultation, and in addition, foster the teaching that it is better to see what she can accomplish rather than what she can endure.

3. The essayist is correct in recommending in doubtful cases the aid of x-ray study. He is also correct in stating its limitations. No diagnostic aid erroneously interpreted causes

supply in the mother's blood stream and the individual villi die immediately. Whether or not the intervillous deposit is absorbed in whole or in part, this local portion of placenta is never restored to vitality. The adjacent fetal blood vessels which supply this portion of the placenta naturally collapse; the muscular walls of the arterioles contract, and an atrophic regressive change takes place in the placental circulation at this point. Peculiar to say, a secondary fibrosis or connective tissue development in this area is rarely seen. Possibly the life span of the placenta is too short for such a reaction to take place.

While it is quite true that these areas of intervillous thrombosis and necrosis occur more frequently in the instance of chronic nephritis complicating pregnancy, eclampsia, and other hypertensive states, yet there has never been any evidence to prove that these lesions are the cause of such complications in the mother.

DR. BARTHOLOMEW (Closing).—I want to comment first on Dr. Reis' remarks about the placental tissue not being necrosed.

Regarding the thought that this disturbance is due to interference with maternal rather than fetal circulation, if one will study the lesion at the point where the infarcted tissue borders on the normal, I do not see how one can come to any other conclusion than that the disturbance is fetal. The vessels of the villi are dilated on one side and sharply across the border the villi are entirely normal. If the disturbance came through the maternal circulation there should be no such line of demarcation. If it came through the maternal circulation all of the villi would be affected.

As to Dr. Montgomery's comment questioning why toxemia does not take place very acutely when the fetus dies and the villous circulation ceases, if one examines these placentas after the baby has been dead several weeks he still finds the villi stain well. The vitality of the villi is dependent upon both the fetal and the maternal blood supply. If the maternal supply is cut off by enlargement and crowding of the villi and there is absolute lack of fetal circulation, necrosis takes place. One does not see tissue breakdown when in a state of acute necrosis. The vessels are thrombosed, the nuclei pyknotic, and the tissue does not take a clear stain. The ones that I showed were acutely infarcted. But here is one that is completely fragmented.

In the last few years infarction has been pigeonholed and I do not think we will ever get anywhere in the solution of toxemia unless we include it in the whole question. Vaso-spasm is an important part of the situation but, to my mind, infarction must be included to furnish the toxic elements responsible for the toxemia.

the lower segment and extraperitoneal operations. The so-called low-flap transverse section is not only a relatively easy procedure but has, in addition to its safety and smoothness of convalescence, an amazingly low incidence of rupture of the uterine scar in subsequent pregnancies. An incidence of 0.26 per cent rupture of lower segment scars in a series of 3,600 sections of the low-flap type reported by Wetterwald, as against an incidence in this country variously reported as ranging from 4 per cent to 10 per cent of ruptures in classical scars is tragically significant. I am of the opinion that the extraperitoneal operation should be reserved generally, in the average clinic, for potentially infected cases.

A review of cesarean sections at the Memorial Hospital in Worcester during the fifteen-year period covered by Dr. Hennessy's paper shows that 821 sections were performed in 11,560 deliveries, an incidence of 7 per cent. There were three deaths in this series—one due to shock following abruptio placentae, one due to hemorrhage associated with placenta previa and the third, which occurred on the eighteenth postpartum day, due to pulmonary embolism. Two of these deaths followed low-flap operations. The mortality for the series was 0.036 per cent.

The sections were performed by six operators. More than 95 per cent were done by four obstetricians. In this series, there were three extraperitoneal sections, 59 classical sections and 762 low-flap sections.

The high incidence of cesarean sections in a hospital is probably due to: first, a top-heavy private service; second, the reference to the clinic as a consulting service of a number of potential cesarean cases; and finally, a clinic record of low maternal mortality.

DR. ALFRED L. POTTER, Providence, R. I.—Dr. Hennessy's results move me to ask that this Society help hold up the hands of others who are also trying to establish or maintain an "F.E.P.A.," a Fair Employment Practice Act for obstetrics—a reasonable and proper cesarean section incidence rate. With the authority of this organization behind us, those of us whose duty it is to direct them will better be able to control the *furor operandi* of more radical and inexperienced staff members of our hospitals.

By the same token I ask that, in the attempt to make Dr. Hennessy's results common elsewhere, this Society completely outlaw the use of the classical cesarean section. At the Providence (R. I.) Lying-in Hospital, in 47,885 confinements from 1938 to 1947, inclusive, there were 1,465 sections by 20 operators, an incidence of 3.1 per cent. Only thirteen classical sections were included, and even these were followed by the apologies required following the perpetration of any other equally grave social error. There was one death in the last 1,014 sections.

THE ROLE OF PENICILLIN IN OBSTETRICS*

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PRIOR to the year 1935, sterilization of the blood by chemical means was looked upon as an unattainable ideal, and the occurrence of obstetric complications attended by infection constituted a major hazard reflected in high maternal and fetal morbidity and mortality rates. In 1935, the advent of the sulfonamides represented the first of the chemotherapeutic agents and probably the greatest therapeutic discovery in modern medicine. While the sulfonamides served as a powerful weapon for combating infections in general at a time when such a drug was so much in demand, there remained much to be desired to meet all the requirements, more especially those problems of infection in the field of obstetrics. It is believed, from experience gained thus far in its use, that penicillin will solve many of these problems.

Relative Freedom From Undesirable Reactions

Experience with the sulfonamide preparations has demonstrated their limitations and contraindications in the presence of such conditions as severe anemia, nephritis, hepatitis, agranulocytosis and nausea, as well as their incompatibility with other drugs.

The purpose of this paper is to present some of the advantages offered by penicillin in the treatment of infections in pregnancy and its use in the management of obstetrical difficulties. From a review of the literature and from a study made during the past two years, it is desired to point out the wide therapeutic range of penicillin and its freedom from toxic and undesirable side reactions as well as its compatibility with other therapeutic agents.

Within the first year or two following discovery of the valuable antibacterial properties of penicillin and its use as a therapeutic agent, the question was raised by Stokes and others^{1, 2, 3} as to its possible abortifacient action. It is significant that clinical observations made at that time of cases of threatened and actual abortion complicating the administration of penicillin in pregnancy were made in the early days of its usage and primarily on patients undergoing antisyphilitic treatment. It is now believed that those untoward reactions resulted not so much from the penicillin itself, but from the impurities contained in the commercial product prior to proper standardization.⁴ It also seems significant that reports of the possible action of penicillin in stimulating uterine contractions to produce abnormal bleeding and premature labor were the result of observations made on patients under antisyphilitic treatment. Such reactions have since been interpreted as a "form of therapeutic shock or Herxheimer reaction."⁵

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In our experience there is nothing which suggests that penicillin has oxytocic or abortifacient properties. A summary of the fifty-eight patients who were treated with penicillin during their antenatal course is presented in Table I. The mode of administration in this series, as in nearly all of our patients, was the three-hourly intramuscular injection, and the penicillin used was crystalline penicillin G sodium in aqueous solution. As a result of reports in the literature by Hesseltine⁶ and others, and from our own studies of blood concentrations and organism sensitivity, the administration of large doses, 50,000 to 100,000 units per injection, depending on the nature and severity of the infection, has been the established policy.

TABLE I. PATIENTS GIVEN PENICILLIN DURING PREGNANCY

DIAGNOSIS	TRIMESTER IN WHICH PENICILLIN GIVEN			TOTAL PATIENTS
	1	2	3	
Syphilis	2	4	0	6
Cellulitis or furuncle	2	2	1	5
Otitis media	2	0	0	2
Pharyngitis	2	3	0	5
Upper respiratory infection	1	2	1	4
Acute appendicitis	1	0	0	1
Endocervicitis	2	1	0	3
Pelvic inflammatory disease	7	1	1	9
Vaginitis	0	2	1	3
Cystitis	3	1	1	5
Pyelonephritis	0	3	6	9
Miscellaneous	0	1	5	6
	22	20	16	58

Of these fifty-eight patients, forty-two were in the first or second trimester of pregnancy at the time of treatment. None of these patients exhibited either vaginal bleeding or uterine contractions except three patients who were admitted with threatened abortion. Two of these patients were admitted with threatened abortion and received penicillin for concomitant pelvic inflammatory disease; neither patient aborted. The third patient, five and one-half months pregnant, was admitted with threatened abortion. She had had a polyp removed from the cervix at two and one-half months' gestation. She received penicillin treatment for an endocervicitis, and after three days of such treatment with continued bleeding she aborted a nonviable fetus. This is the only case in our series in which penicillin administration was followed by abortion, and it is at least questionable that penicillin could have been a significant factor in the termination of this pregnancy. We conclude, therefore, that penicillin, that is, the product available for use now, is not an abortifacient and does not have an oxytocic effect upon the uterus.

A review of the records of two hundred mature women patients with histories of normal menstrual cycles who were treated with penicillin revealed no incidence of abnormal uterine bleeding which could be attributed to penicillin therapy. Speiser and Thomas⁷ made similar observations on thirteen hundred patients undergoing penicillin therapy.

Bacterial Sensitivity and Mode of Administration

In cases of infection the importance of bacteriologic diagnosis of the invading organism cannot be overemphasized in view of the wide variations in penicillin sensitivity between various species or within the same group or strain. Clinical observations reveal that penicillin is more lethal for bacteria which stain gram positive than those which stain gram negative and more

effective against gram-positive and gram-negative cocci than against gram-negative bacilli. Table II lists some of the commonly encountered organisms with relative degree of susceptibility to penicillin.

TABLE II. SENSITIVITY OF COMMON ORGANISMS TO PENICILLIN

VERY SENSITIVE (1)	SENSITIVE (2)	RESISTANT (3)	VERY RESISTANT (4)
<i>Corynebacterium diphtheriae</i>	<i>Streptococcus faecalis</i>	<i>Streptococcus pyogenes</i>	<i>Escherichia coli</i>
<i>Staphylococcus albus</i>	<i>Eberthella typhosa</i>	<i>Salmonella schottmüller</i>	<i>Pseudomonas fluorescens</i>
<i>Staphylococcus aureus</i>	<i>Salmonella paratyphi</i>	<i>Shigella dysenteriae</i>	<i>Serratia marcescens</i>
<i>Neisseria gonorrhoeae</i>	<i>Brucella abortus</i>	<i>Neisseria catarrhalis</i>	<i>Aerobacter aerogenes</i>
	<i>Streptococcus hemolyticus</i>		<i>Proteus vulgaris</i>
			<i>Klebsiella pneumoniae</i>
			<i>Haemophilus pertussis</i>
			<i>Monilia albicans</i>

(1) Complete in vitro inhibition from 0.01 to 0.05 unit/ml.

(2) Complete in vitro inhibition from 0.1 to 2.5 units/ml.

(3) Complete in vitro inhibition from 5.0 to 20.0 units/ml.

(4) Complete in vitro inhibition requires 40 or more units/ml.

The degree of penicillin sensitivity is expressed in terms of the smallest number of units per c.c. of serum required to inhibit growth of the organism and may vary from 0.03 unit per c.c. to 20 or more units per c.c. Clinical observation and laboratory investigations indicate that penicillin resistance may rise with inadequate dosage. The objective in penicillin therapy, once procedures are started for bacteriologic diagnosis and sensitivity, is to establish and maintain a blood concentration above that considered clinically necessary to destroy the offending pathogen. In our experience maximal therapeutic efficiency has been obtained in the average infection by the three-hourly intramuscular injection of 50,000 to 100,000 units of penicillin in aqueous solution.

Blood level determinations have been considered of therapeutic significance in that they provide the following information: (1) when penicillin is present at maximally effective bacteriostatic concentrations; (2) when concentrations are lower, more slowly bacteriostatic concentrations are found; and (3) when concentrations are not sufficient to inhibit growth in vitro but great enough to act in vivo.³ This explains the apparent discrepancy between reported in vitro sensitivities and the clinical response of the infectious process in many cases of infection with "resistant" organisms.

Penicillin differs in its action from that of the general protoplasmic poisons, such as certain halogens, heavy metals, and phenols, in that it interferes with a specific biologic mechanism in the growth process of a select group of organisms, causing ultimate destruction. The action of penicillin is exerted directly on the invading organism and is, therefore, not dependent upon interaction with the bodily defense mechanisms. Very high concentrations of penicillin may also be bacteriocidal to some organisms. Since penicillin has been found to be virtually nontoxic, it may be administered by any known avenue or route which will bring it in contact with the pathogen.

The intramuscular route is the method of choice in the average or more severe infections. On our service, all cases which require penicillin are admitted to the hospital in order that they may receive injections every three hours. The continuous intramuscular drip may be used in more severe infections where higher and more sustained levels are required.

Intravenous administration has been reserved for overwhelming infections where exceptionally rapid and high blood levels are desired. By the continuous intravenous drip penicillin enters the blood stream continuously and produces high levels despite its rapid excretion by the kidneys.

Subcutaneous administration of penicillin in aqueous solution is feasible with the highly purified crystalline preparations now available. The rate of absorption is slower than with the intramuscular and intravenous routes and blood levels are uncertain. There may also be pain at the site of injection.

Topical applications in the form of aqueous solutions or in ointment have a limited use, thus far, in obstetrics, due to local reactions, sensitization and uncertainty as to absorption and concentration. The study by Rock and associates¹⁰ clarified the question and absorption per vagina. They have shown that except during the last two months of pregnancy therapeutic blood levels can be maintained by this mode of administration. A study of the use of vaginal suppositories for the prevention of postpartum morbidity has been recently reported by Pierce.⁹

Results

In an effort to evaluate our results with penicillin treatment in infections complicating pregnancy, the records of one thousand consecutive admissions to the obstetrical service were reviewed. Cases not included here were admissions for observation of patients with such complications as toxemia, nervous disorders, and other conditions not on an infectious basis. These cases are presented in Table III. For purposes of comparison, all patients admitted with these diagnoses were included, whether or not infection was present.

TABLE III. 1,000 OBSTETRIC ADMISSIONS

CASES ADMITTED ANTEPARTUM	PENICILLIN GIVEN	PENICILLIN NOT GIVEN	TOTAL
Abortion	32	27	59
Threatened abortion	2	25	27
Urinary tract infection	16	4	20
Genital tract infection	9	0	9
Syphilis	6	0	6
Incidental infections	25	0	25
Total this group	90	56	146
CASES ADMITTED INTRAPARTUM			
Normal	0	736	736
Mastitis	24	0	24
Genital tract infections	20	3	23
Urinary tract infections	10	8	18
Prophylactic penicillin	27	0	27
Incidental infections	5	0	5
Cesarean section	14	7	21
Total this group	100	754	854
Total both groups	190	810	1000

Under "Abortion" are included all cases in which pregnancy was terminated before the age of viability and includes both complete and incomplete abortions. The classification, "Threatened Abortions," includes all cases within the first and second trimester admitted with vaginal bleeding, with or without abdominal cramps, and includes some cases in which infection was present. "Genital Tract Infection" includes all cases with infection

in the reproductive tract except those in which threatened abortion was the chief complaint. The group of "Incidental Infections" includes a variety of types of infection not related to the pregnancy except by coincidence. These are included in Table I.

The second category, "Cases Admitted Intrapartum," includes all patients who were delivered of a viable infant. Only those cases were considered to be "Normal" who exhibited no evidence of infection, did not receive penicillin or other specific chemotherapy, and who had no temperature elevation sufficient to be classed as "morbid." The group of genital tract infections includes pelvic cellulitis and perineal infections following episiotomy, as well as frank endometritis. Those patients listed under "Prophylactic Penicillin" received this drug for a variety of reasons; these indications are tabulated in Table IV. The classification, "Incidental Infections," again includes that group of patients who had infectious processes not related to the pregnancy, and all those in this category had upper respiratory infections.

"Cesarean Sections" are listed separately because it was felt that these constitute a special complication and that the results in these cases should be considered apart from the vaginally delivered patients.

TABLE IV. CASES RECEIVING PROPHYLACTIC PENICILLIN

INDICATION	NUMBER CASES	AVERAGE DOSE	AVERAGE TOTAL	NUMBER MORBID	COMMENT
Antepartum gonorrhea	1	30	1.5	1	Temp. to 102° F. 3rd postpartum day, 101° F. 4th postpartum day, normal 4th postpartum day
Uterus packed	9	60	1.4	0	6 patients temp. to 100° F. one day only
3rd degree laceration	4	80	2.5	0	Afebrile, no signs of infection
Vaginal examinations before delivery	6	40	0.6	0	2 patients, temp. to 100° F., one day only
Manual removal of placenta	1	40	0.6	0	Afebrile, gross contamination suspected
Premature rupture of membranes	6	80	3.2	0	1 patient temp. rise to 100° F. one day only
Total cases	27	--	--	1	

Indications in Treatment and Prophylaxis

The various indications for the prophylactic use of penicillin in patients delivered vaginally are listed in Table IV. These twenty-seven patients constitute 3.2 per cent of the vaginally delivered cases. Only one patient had a morbid puerperium. She had acute gonorrhea during the eighth month of pregnancy, and received 30,000 units dosage of penicillin for a total of 3.2 million units during the acute phase of the infection with apparent recovery except for a moderately profuse nonspecific vaginitis. When this patient was admitted in labor, penicillin was again begun in 30,000 units dosage and was given for six days. In spite of this she had a morbid course with temperature to 102° F. on the third postpartum day and 101° F. on the fourth postpartum day with the usual signs and symptoms of acute endometritis. It is probable that the 30,000 unit dosage used at the time of delivery in this patient was inadequate, and suggests that some resistance to penicillin had been acquired by the organisms responsible for her vaginitis. This does not

reflect our current policy in this respect. During the past six months we have administered 100,000 units every three hours as the prophylactic dose whenever such prophylaxis was thought indicated. In general, the results as presented in Table IV were satisfactory since in all of these situations the likelihood of infection is, theoretically at least, much increased.

While it is true, as pointed out by Mengert,¹¹ that basic causes of intra-uterine fetal death remain largely unknown, infection as a possible cause has received relatively brief mention in the literature. Again referring to Doctor Mengert's paper he listed infection as the cause of fetal and neonatal death in 8.1 per cent and 4.7 per cent in Sloane and Chicago Lying-in Hospitals, respectively.

In 1945, Douglas and Davis¹² pointed out the value of prophylaxis in puerperal infection over any known curative agent once the disease was established and stated at that time "that sulfadiazene or penicillin given early may be efficacious, while late in the course of the disease they may be relatively ineffective." Since then, some very interesting work has been done on the bacteriology of the uterus during labor and the puerperium. Guilbeau¹³ and others on Doctor Eastman's service at Johns Hopkins Hospital have just completed a study of the effect of penicillin on the bacterial flora of the postpartum uterus. This investigation consisted of a study of the uterine cultures from eighty-six postpartum patients and indicates that relatively high doses of penicillin administered pre- and postpartum may eliminate penicillin-sensitive organisms from the postpartum uterus for seventy-two hours or longer. Even single doses, given early in labor, may be effective forty-eight hours after delivery. This very excellent work not only helps to confirm the opinion that penicillin therapy is more effective when instituted early, but will undoubtedly stimulate further interest in the study of the prophylactic use of penicillin in obstetrics.

TABLE V. CESAREAN SECTIONS

	MORBID				NOT MORBID				TOTAL		
	A		B		A		B		TOTAL	MORBID	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	NO.	PER CENT
Section during labor	2	9.5	0	0	2	9.5	1	4.8	5	2	40.0
Elective section	3	14.3	1	4.8	7	33.3	5	23.8	16	4	25.0
	5	23.8	1	4.8	9	42.8	6	28.6	21	6	28.5

A, with penicillin.
B, without penicillin.

Table V lists the patients who were delivered by cesarean section. The section rate, 2.46 per cent, is comparable to the over-all section rate for this hospital, 2.66 per cent. It is interesting to note the increased morbidity among those patients who were sectioned after labor had started, namely, 40 per cent in that group, as compared to 25 per cent in the group sectioned electively before the onset of labor. This suggests that the onset of labor is a factor in the spread of infection as reported by Guilbeau. Most probably this related to the extension of pathogenic organisms from the lower reproductive tract to the interior of the uterus and probbaly also to the parametrial tissue. The incidence of morbid patients in this group who had received penicillin, as compared to those who had not, would seem to contradict our thesis that penicillin is efficacious in reducing the effects of an infectious

process. However, those patients who received penicillin were, for the most part, obviously infected before delivery was accomplished. Also, during the early part of the series relatively small dosages of penicillin were given, namely 30,000 or 40,000 units every three hours. Since we have begun to use large doses of penicillin, that is, 100,000 units every three hours, the results have been much more gratifying. This series of twenty-one sections is, of course, too small to permit any statistically sound comparison. It is, however, interesting to note that among the fourteen patients in whom there was an indication for penicillin treatment, only about one-third actually had a morbid postoperative course.

Advantage of Adequate Dosage

Among the vaginally delivered patients, thirty-three, or 3.96 per cent, had puerperal morbidity (see Table VI). The largest group of morbidity was in a series of patients having mastitis. Two patients of this group were of special interest. These women had acute mastitis eight and eleven days, respectively, after delivery and were treated with 40,000 units of penicillin every three hours for a total of 800,000 units, and both had a fall of the temperature to normal within thirty-six hours. Both of these patients, however, had recurrences of the infection in the same breast within four days after the initial course of penicillin was discontinued. The second course of penicillin therapy consisted of 100,000 units every three hours for periods of four and five days, respectively. Both patients had a good clinical response and no further recurrences. We have noted that in cases of mastitis the most important factor as regards the duration of the febrile reaction and of course, concomitantly, the toxicity of the patient, is the time at which penicillin treatment was started, as was concluded by Douglas.¹² This factor seems to have been of more importance than the dosage. When penicillin was begun with the earliest signs of inflammation in the breast, the clinical course was much more benign than in those patients who had developed a marked febrile reaction before the onset of therapy. The infections cleared more rapidly, and there was less induration in the first group of patients. The dose of penicillin used seemed by and large to be related to the rapidity with which the inflammatory process resolved; that is, the period of convalescence was less and the duration of definite indurated areas was less in most patients receiving large doses. There was no case of recurrence in any patient who had received either 80,000 or 100,000 units of penicillin during the initial course of treatment.

TABLE VI. POSTPARTUM MORBIDITY

DIAGNOSIS	NUMBER OF CASES				TOTAL	
	MORBID		NOT MORBID			
	A	B	A	B	NO.	PER CENT MORBID
Normal	-	-	-	736	736	0
Mastitis	18	0	6	0	24	75
Endometritis	3	0	5	2	10	30
Pelvic cellulitis	2	3	3	0	8	63
Perineal infection	2	0	3	0	5	40
Urinary tract infection	2	2	8	6	18	22
Prophylactic penicillin	1	0	26	-	27	4
Upper respiratory infection	0	0	5	-	5	0
Total	28	5	56	744	833	3.96

A, with penicillin.

B, without penicillin.

We should like to note here that we are opposed to the practice of reducing the dose of penicillin when the acute phase of an infectious process has apparently been overcome. We believe that this will increase the incidence of recurrence since organisms beginning to develop a resistance to penicillin will not be affected when the smaller dose is used. It will be noted from Table VI that all patients with mastitis received penicillin treatment. In this small series of twenty-four cases there was no patient who developed abscess. It should be further noted that penicillin was the only specific treatment used in these cases; neither sulfonamides nor x-ray was employed as an adjuvant. We believe that the high incidence of morbidity in this group of infections in spite of penicillin treatment is only a reflection of the seriousness of the condition.

Selective Action of Penicillin

The group of pelvic infections, i.e., endometritis, pelvic cellulitis, and perineal infection, is interesting in view of the response which these patients made to penicillin treatment. In endometritis the principal offending organism was *Staphylococcus aureus* in those cases which were not morbid and *E. coli* in all three cases which were morbid. It will be noted that these three patients all received penicillin. In perineal infections the organism was *E. coli* in both morbid cases and one of the cases which was not morbid, and a nonhemolytic streptococcus in the other two cases which were not morbid. Cases of pelvic cellulitis include those patients without definite signs of endometritis, but who did have lower abdominal tenderness and fever. In three cases large doses of penicillin were given with the onset of the earliest signs with a good response. In two patients penicillin was started only after two days of fever, and they also made a good clinical response. Three patients had relatively low grade fevers, 100.6° F. and 100.8° F. for two or three days with minimal signs, and were not treated with penicillin, but received sulfonamides.

Among the urinary tract infections, two out of the ten cases receiving penicillin were morbid. In these two cases sulfonamides were not given. In the eight cases which were not morbid, five had received sulfonamides and three had not. The two morbid patients with urinary infections who did not receive penicillin both received sulfonamide therapy.

The upper respiratory infections, five in number, all received penicillin treatment with the earliest signs of the disorder. All made excellent clinical response.

In reviewing these cases, several things seem to be suggested. First, in urinary infection, sulfonamides were apparently of more therapeutic value than was penicillin, even in large doses. Second, with a frank endometritis large doses given early were effective except in those cases in which *E. coli* was present, and in those penicillin seemed to be relatively ineffective. Third, in the group of perineal infections, the same situation obtains. This would seem to indicate that in postpartum infections the important factors are first, early treatment with adequate dosage of penicillin, and second, recognition of those cases in which a penicillin-resistant organism is present, and in such cases to use other drugs in addition to penicillin. We believe that penicillin is indicated in all cases of puerperal infection even when the principal pathogen present is known to be penicillin resistant. This means the effects of other organisms present will be kept at a minimum. Treatment should, of course, be instituted to combat the penicillin-resistant organisms.

Pelvic Infection and Abortion

In our clinic we see a large number of patients who have pelvic inflammatory disease. Most of these patients have a relatively benign type of infection, chronic in nature, and these we classify as low grade types of infection. They rarely develop an acute exacerbation. It was our impression in the clinic and on the gynecological and obstetrical services, that many patients with this type of infection presented fertility problems and that abortions and threatened abortions were fairly frequent. It was thought, therefore, that perhaps the infectious process, per se, was a significant factor in these two conditions. If this were true, elimination of such an infectious process could probably be of benefit both as regards fertility and in the occurrence of abortion. We have no figures available on the effect, if any, of penicillin on patients with infertility problems, but it was possible to analyze our series of hospital cases of abortions, complete, incomplete, and threatened, with regard to the occurrence of concomitant pelvic inflammatory disease and in respect to the effect of penicillin treatment. These figures are presented in Table VII. It will be noted that eighty-six patients are included in this series. Of these, fifty, or 58 per cent, had clinically recognizable pelvic inflammatory disease, while thirty-six, or 42 per cent, did not. Among the first group of patients who aborted—including complete abortion or incomplete abortion necessitating dilatation and curettage—there were a total of fifty-nine cases. Of these fifty-nine, thirty-two patients had pelvic inflammatory disease and twenty-seven did not, or 54 per cent and 46 per cent, respectively. Among patients without pelvic inflammatory disease none received penicillin before abortion, and among the patients with pelvic inflammatory disease, only one patient had received penicillin before abortion (v.s.). In the group of patients with threatened abortions, nine were without pelvic inflammatory disease and eighteen patients had pelvic inflammatory disease. In the former group no patient received penicillin treatment. In the latter group two patients did receive penicillin.

TABLE VII. PELVIC INFECTION AS A FACTOR IN ABORTION

		A ¹						B						TOTAL	
		TOTAL		A		B		TOTAL		A		B		A	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Abortion	59	1	1.2	1	1.2	0	-	58	67.5	31	36.1	27	31.4	32	37.3
Threatened abortion	27	2	2.3	2	2.3	0	-	25	29.0	16	18.6	9	10.5	18	20.9
	86	3	3.5	3	3.5	0	-	83	96.5	47	54.7	36	41.9	50	58.2

¹Under "AB" only those patients are included who received penicillin before abortion occurred.

A, with penicillin.
B, without penicillin.
a, with pelvic inflammatory disease.
b, without pelvic inflammatory disease.

An analysis of these figures can only suggest a relationship since the series is very small but the suggestions are quite definite. The fact that there is a relatively small difference between the number of patients with and without pelvic infection who aborted would indicate that probably this infection was not the most important factor but that such abnormalities as defective ova and faulty implantation were more significant. However, among the patients with threatened abortion, the difference between these groups is considerable. Twice as many patients had pelvic infections as did not. This tends to sup-

GYNANDROBLASTOMA OF THE OVARY*

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FEMINIZING tumors of the ovary, the granulosa-thecomatous group, may now be considered fairly common tumors of the ovary. Novak¹ states that granulosa-cell carcinoma constitutes about 10 per cent of all the solid malignant tumors of the ovary. The thecomatous tumor is much less frequent. Masculinizing tumors of the ovary on the other hand are rare; a total of about 76 cases have been reported in the literature. A combination of feminizing and masculinizing elements in an ovarian tumor was first described by Robert Meyer² in 1930. He coined the term gynandroblastoma for this composite type of ovarian tumor.

A survey of the literature reveals a total of 21 cases described, namely, by Meyer,² Tietze,³ Amati,⁴ Schiller,⁵ Eerland and Vos,⁶ Frankl,⁷ Bergstrand,⁸ Plate,⁹ and Mechler and Black.¹⁰ A critical review of these case reports leaves considerable doubt as to whether several of the tumors meet the criteria for the diagnosis of gynandroblastoma. Mechler and Black likewise have deleted several of these cases on the basis of lack of conformation to histologic and biologic criteria. Schiller¹¹ has accepted only four of the above mentioned cases for inclusion in this category.

The subsequent case report represents such a lesion. There has been repeated opportunity to study this patient, clinically, pathologically, and endocrinologically, over a period of about two and one-half years. She has already had four laparotomies, three for recurrence of the tumor. There are so many unusual features to this case it seems advisable to report it in some detail.

Case Report

First Hospital Admission.—An 18-year-old, virgin girl entered Barnes Hospital Dec. 8, 1945, with chief complaints of amenorrhea for three years, rapid weight gain, and marked increase in size of abdomen three weeks prior to admission to the hospital. Menarche at age 13, with a regular twenty-eight-day cycle lasting four to five days with moderate flow. After about one and one-half years of a regular cycle, she suddenly became amenorrheic and had not menstruated for three years. She noticed breast development during the time she was menstruating, but on cessation of her menses breast development stopped; however, there was no decrease in size. The patient stated, and it was confirmed by her mother, that since onset of amenorrhea she noted her voice had become deeper in pitch; increase and darkening of hair of face, and increased growth of pubic and leg hair. An "electrologist" removed hair on her face one year ago and she had to shave her legs. She had had a pelvic examination by her local physician one year ago and was told she was normal. Psychologically she had a masculine attitude. Her mother stated she preferred to associate and play games with boys rather than associate with girls of her age. Her family and past history were irrelevant. About three weeks before admission she had gained ten pounds in one week. Concomitant with her weight increase, she observed rapid increase in size of her abdomen which she considered

*Presented by invitation, at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

Discussion

Dr. R. T. LAVAKE, Minneapolis, Minn.—Drs. Harris and Shook have emphasized what our experience would corroborate: that pregnancy is not a contraindication to the use of penicillin, and that the earlier it is administered the more effective it tends to be, and that the dosage should be adequate from the beginning. The method of administration and dosage outlined has in our experience given excellent results.

Now in regards to when to stop the penicillin. We have found that it is well to continue the penicillin until all visual and palpatory signs of the inflammation have subsided and temperature and leucocyte count have been normal for forty-eight hours. It is hoped that there will be more discussion on this important point.

That the incidence of abortion is definitely increased by all types of infection is borne out by clinical experience; and serologic data has suggested the likely mechanism that brings about this increase. It seems, therefore, that the essayists are logical in their reasoning that by eliminating infection by penicillin the incidence of abortion should be reduced. The prevention and elimination of infection in pregnancy has been an essential part of prenatal care for many years, with the lessening of abortion incidence as one of its major aims.

It would seem from Dr. Harris's cesarean statistics that he wishes to make it clear that the idea of prophylactic penicillin should not lead one to change in any way one's rules governing the safest condition, method, and time for performing cesarean; and that the idea should not be interpreted as permitting any reduction in previously recognized standards favoring perfect asepsis or as permitting increased latitude in regard to the safety of operative interference. With these views we heartily concur.

It has been our experience also that urinary infections are most frequently of a type more amenable to the sulfonamides than to penicillin. Thus, the sulfonamides are tried first before results from cultures can be obtained and, if ineffective, penicillin is substituted.

DR. LOUIS DOUGLAS, Baltimore, Md.—Among the statements which Dr. Harris makes there are several which will bear repeating for the sake of emphasis: First, penicillin is not a panacea for all types of infection met with in obstetrics. There are organisms which are extremely resistant to the drug and little or no benefit would follow its use when dealing with infections from these. Therefore, cultures should be obtained at the onset of treatment and additional therapy added when indicated or, better still, since the colon bacillus is so frequently encountered, one of the sulfonamides might be included at the beginning of treatment. This is a point which has been and still is woefully neglected in many places. When the essayist speaks of the prophylactic use of penicillin, it would appear that he has learned well the inadequacy of small doses and at the present time is actually using it therapeutically; and this is as it should be. When a patient is potentially or actually infected, it means that her tissues are being invaded by pathogenic organisms of unknown virulence and susceptibility to penicillin. Since it is safe to use, in large dosage, it would seem better judgment to give enough to care for all contingencies. In this way there will also be much less danger of resistance to the drug occurring.

Captain Harris, when he speaks of cesarean section, does not state whether these were classical, low, or extraperitoneal, and in this he is probably wise since the relative safety of these various approaches is still being debated. Probably the simplest conclusion today is that, in the presence of infection, any type of section is hazardous, and that the sulfonamides and penicillin have materially reduced the risk but have not completely eliminated it.

The experiments in the use of penicillin in cases of relative sterility and repeated abortions are most interesting and it is to be hoped that the work will be continued. It might be extended with benefit to include the husbands as well as the wives.

DR. E. D. PLASS, Iowa City, Ia.—In an attempt to determine the effectiveness of penicillin given during labor in reducing the incidence of puerperal febrile reactions, my associate, Doctor W. C. Keettel, carried on a clinical experiment during the year ending in

port the hypothesis stated above. The study of this possible relationship is being continued on our service.

In view of the clinically proved value of penicillin when used alone or as combined therapy in not a few conditions which before its discovery were for the most part treated expectantly—and frequently unsuccessfully—a criticism that it is used promiscuously would seem unjustified. Until an antibiotic or chemotherapeutic agent with superior antibacterial activity and with equal freedom from toxicity is discovered, it is believed that penicillin administered for the proper indications, either prophylactically or early in the course of infectious disease, and in adequate dosage will continue to serve in revolutionizing the management of obstetrical problems attended by infection.

Summary and Conclusions

1. The advantages in the use of penicillin in obstetrics over other chemotherapeutic agents are discussed, as well as its efficacy and compatibility with other agents in combined therapy.

2. The possibility of abortifacient or oxytocic properties of penicillin is discussed, and clinical evidence is presented which suggests that such reaction reported early in its use, for the most part in patients undergoing antisyphilitic treatment, was the result of impurities in the drug or of therapeutic shock.

3. The significance of bacteriologic diagnosis and sensitivity is discussed with their relation to dosage and therapeutic efficiency of penicillin. Penicillin resistance may rise in the presence of inadequate dosage.

4. The modes of administration and relative efficacy are discussed. The intramuscular route has been found to be the method of choice in all but the most severe infections.

5. An evaluation of the results of penicillin therapy in the various infections complicating pregnancy is presented in a statistical analysis. The value of the prophylactic and very early use of penicillin in sufficiently large doses when it is indicated has been fairly well established.

6. The possibility that pelvic inflammatory disease might be a factor in certain cases of infertility and in some cases of premature termination of pregnancy is suggested. While there are insufficient data from the study to prove such a thesis, further investigation may reveal that such infections are sufficient indications for active therapy. With our present armamentarium, this includes penicillin.

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twelve hours or more, or who in any way seems to be headed for trouble, should have penicillin administered prophylactically. This is especially advisable if there is any likelihood of cesarean section being performed.

DR. OTTO H. SCHWARZ, St. Louis, Mo.—Bacteriologic studies done years ago, not only in our clinic but at New York Lying-In, Hopkins, and Chicago Lying-in, showed very conclusively that anaerobic streptococci are the chief offending organisms in such services. I have for some time made an effort to find out just what the penicillin would do to the anaerobic streptococci and found nothing definite. Sulfonamides are of no use against anaerobic streptococci. Dr. Plass stated that they are not sensitive to penicillin, and Dr. Eastman pointed out they were. This causes further confusion, but since Dr. Eastman's statement is based on actual bacteriological work, we must accept it.

DR. HARRIS (Closing).—Dr. LaVake has raised the question as to what constitutes adequate penicillin therapy. In our experience the indications for discontinuing the drug after the acute signs and symptoms of infection subside depend upon the condition. We believe the practice of reducing the dosage when the acute phase has apparently been overcome will increase the incidence of recurrence, since organisms which develop a degree of resistance to penicillin will not be affected by the smaller dose.

In reply to Dr. Douglas: All our cesarean sections were of the low cervical type except one classical in a patient who had a history of a previous classical section.

From the interesting work they are doing with penicillin in obstetrics, the remarks by Dr. Eastman and Dr. Plass are a real contribution.

February, 1948. Alternate patients were given 300,000 or 600,000 units of penicillin in oil and wax as soon as they were definitely in labor, and 300,000 units every twenty-four hours thereafter until delivery, with a single 300,000 unit dose post partum, twenty-four hours after the last antepartum injection. There were 465 patients in this series and 430 in the control group which received no antepartum antibiotics.

All temperatures were taken by mouth five times daily, every four hours except at 2:00 A.M. Any elevation to 100.4° F. or higher was considered febrile. "One-day fever" was diagnosed when the elevation persisted for less than twenty-four hours. The same criterion was employed in determining "intrapartum fever."

There was no significant difference in the incidence of "one-day fevers" and "intrapartum fevers" in the two groups, possibly indicating that they are not commonly due to infections, or that, if infectious in origin, the etiologic organisms are not penicillin sensitive.

Two-or-more-day fevers occurred in 10.2 per cent of the control series, as against 7.0 per cent in those receiving an initial penicillin dose of 300,000 units, and 3.0 per cent for the series given 600,000 units at the onset of labor. In the whole series there were twelve untreated patients who had fever for more than three days, as compared with only two in the treated series. This appears to indicate that the more persistent puerperal fevers are more likely to be due to aerobic gram-positive bacteria that are sensitive to penicillin. The evidence also appears to support the concept that a fair proportion of postpartum infections of the generative tract are the result of the invasion of anaerobic bacteria that generally are resistant to penicillin.

This work is being continued in an effort to determine whether there is any value in prophylactic administration of this antibiotic to normal women with the prospect of normal parturition. At present, we are skeptical. On the other hand, we are already convinced that in prolonged labor, the exhibition of penicillin is reasonable and probably useful, particularly for the protection of the child from the dangers of amnionitis.

On the basis of our limited experience, we are also impressed by the value of antepartum penicillin injections as a means of eye prophylaxis in the newborn. Conjunctivitis neonatorum appears to be less common following this form of indirect prophylaxis than after local applications of either 1 per cent silver nitrate solution or of penicillin-containing ointment.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—On Jan. 1, 1947, we initiated a study on the efficacy of penicillin as a substitute for silver nitrate in the prophylaxis of gonorrheal ophthalmia. The object of that study, of course, had to do with ophthalmia and not with puerperal infection, but we were interested to know the results with regard to the latter. Each mother received 200,000 units of penicillin intramuscularly at the onset of labor. If her labor extended beyond eighteen hours, this was repeated. Our puerperal morbidity in 1947, judged by usual standards, was 3.8 per cent. In 1946 our puerperal morbidity had been 8.2 per cent, and in 1945, 9 per cent, and has never been below a figure of 8 or 9 per cent except for the year of 1947.

After trying to explore other explanations for this reduction of puerperal morbidity by one-half, we felt that the injection of penicillin was probably the factor. Some plausibility to this hypothesis was lent by the following circumstance. On Jan. 1, 1948, we gave up the maternal injection of penicillin in labor and, for the first six months of this year, our puerperal morbidity has returned to the previous figure of 8 or 9 per cent. This is in agreement with Dr. Plass's report, and it was this clinical study that led us to the laboratory and prompted the study that Dr. Guilbeau and his associates made and which Dr. Harris referred to this morning. They found that puerperal uterine cultures were sterile in 75 per cent of patients to whom penicillin had been administered routinely in labor, whereas in patients who had not received penicillin the great majority showed pathologic organisms. This leads us to believe that penicillin is lethal to most organisms that commonly cause puerperal infection. The clinical implications are plain enough; and it is our feeling that any woman who has been in labor for eighteen hours or more, or any woman who has ruptured membranes for

in this communication to report our results. During this time we were also developing the use of continuous caudal analgesia in vaginal delivery and we extended its use to cesarean section in 162 patients, without a maternal death. We decided, however, that the continuous or fractional spinal was more applicable because of its simplicity of technique and the saving of time in waiting for the anesthetic level to be reached before operation could be performed. In using continuous caudal analgesia, an average of thirty-one minutes elapsed between the initial injection and the time the patient was ready to be moved to the operating room. In the use of spinal anesthesia there is usually only a waiting period of eight or ten minutes. Our results in continuous caudal, as previously reported, were satisfactory from the standpoint of both the mother and the child. During the period from January 1, 1941, to June 1, 1948, cesarean section was employed as the method of delivery in 1,378 patients. Because this communication is a report of our observations of continuous spinal anesthesia, we shall disregard an analysis of the 378 patients to whom other types of anesthesia were administered.

TABLE II

Total number of deliveries	18,980
Total number of cesarean sections	1,378
Incidence of cesarean sections	7.2%
Total incidence of cesarean sections from 1929 to 1948	6.3%

Our incidence of cesarean section during this interval of seven and one-half years was 7.2 per cent, while the incidence for the nineteen years between 1929 and 1948 was 6.3 per cent. This incidence of cesarean section is high when compared with other statistics and there are several relevant factors which we believe should be pointed out. Our hospital admissions in this Division average about 65 per cent private patients and 35 per cent ward or service cases. Our staff is composed entirely of men who are recognized in our community as specialists and, therefore, a large number of patients are referred to them by outside physicians who have already recognized some abnormality necessitating abdominal delivery. Furthermore, during the last ten years we have increased our incidence of cesarean section in both abruptio and placenta previa and, contrary to opinions expressed recently by well-known authorities, our tabulated results showed an improvement over the results obtained by the more conservative treatment of these conditions. Again, we have increased our incidence of cesareans in pre-eclamptic toxemia where interruption of the pregnancy becomes a necessity and where the baby is almost always premature. We believe that cesarean section in these patients has been directly responsible for the salvaging of many more of these premature babies. We have also adopted the policy of doing a repeat cesarean in most cases, regardless of the indication for the first cesarean. For many years we did not adhere to the dictum, "once a cesarean, always a cesarean," and allowed many of our patients who had had a previous cesarean section for a temporary indication, such as placenta previa, to deliver vaginally. The stress and strain on the accoucheur during these labors and a few disastrous results from ruptured uteri caused us gradually to become believers in repeat cesarean sections. Occasionally, where the baby is small and the cervix is dilated or is easily dilatable, we do deliver the patient vaginally but the majority of subsequent deliveries are by the abdominal route.

In Table III we have shown the various types of anesthesia used but if we had included those patients operated upon under fractional spinal by members of our staff in other institutions, the series would total approximately 1,100 with no additional maternal deaths.

CONTINUOUS SPINAL ANESTHESIA IN CESAREAN SECTION*

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DURING the past decade there has been a very marked improvement in the scientific management of women during pregnancy and parturition, which has resulted in a noticeable decrease in maternal mortality. A report of one thousand cesarean sections performed under one type of anesthesia presents only a part of this general picture and a few of the more pertinent factors which our study elicited are shown in Table I.

TABLE I.

<i>In the last ten years there has been:</i>
a 72 per cent decrease in over-all maternal mortality.
a 91 per cent decrease in maternal mortality from infection.
a 77 per cent decrease in maternal mortality from hemorrhage.
a 73 per cent decrease in maternal mortality from toxemia.
a 23 per cent decrease in maternal mortality from heart disease.
<i>Among cesarean sections in the last ten years there has been:</i>
an increase of 127 per cent in the use of low-type sections.
<i>From 1943 until the present there were:</i>
0 maternal deaths from infection.
<i>In the last five years there were:</i>
0 maternal deaths from hemorrhage.
<i>In the last 1,628 cesarean sections there have been:</i>
0 deaths from anesthesia.

It is noted that in the last 1,628 cesarean sections performed, there has been no death attributable to anesthesia. The last death from anesthesia occurred in 1938, when a very high-strung, nervous individual was given Avertin before being taken from her room to the operating theater. This patient died very suddenly while being transferred to the operating table. Following Lemmon's introduction of fractional spinal anesthesia into general surgery in 1939, we began to consider its use in cesarean section. Our experience with single-dose spinal had not been too satisfactory and we had discontinued its use about ten years prior to this date. During this interval we had performed most of our cesarean sections, when possible, under local or some form of general inhalation anesthesia, usually nitrous oxide and oxygen. It had been our experience that most of the babies born to mothers who had been deeply anesthetized, particularly with ether, at the time of cesarean section, had to be resuscitated immediately following birth, while those babies born to mothers who had local infiltration anesthesia for cesarean section, usually cried immediately. It was, therefore, more in the interest of the baby, than for the sake of the advantages to the mother, that we began in 1941 to use fractional spinal as the anesthesia of choice in our cesarean section patients. Up to June 1, 1948, we had performed 1,000 cesarean sections using this technique and it is our purpose

*Presented at the Fifty-ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 9 to 11, 1948.

c.c. of spinal fluid at the end of the operation which were found to contain anywhere from 7 to 20 per cent of the drug used. Therefore, if a circulatory collapse should occur, the withdrawal of the spinal fluid would also remove part of the anesthetic agent. Table V shows the average drop in systolic pressure in this series.

Table VI shows the average dosage of the drug used. In this series there were 71 cesareans in which only 15 to 30 mg. of the drug were required for the entire operation. We gradually decreased our dosage with the idea that complication would be less likely to develop if less of the drug were used. This we believe is one of the advantages associated with the fractional method. It might be of interest to know that in this group of 1,000 patients, the anesthetic was administered by 38 different individuals, all of whom adhered rigidly to the technique as outlined. The technique of administering continuous spinal anesthesia is as follows:

One hour prior to operation, the patient is given 1.5 grains of the same barbiturate which was given as sedation the previous evening.

One-half hour before operation, the blood pressure is rechecked. If the systolic pressure is below 130 mm. of mercury, a vasopressor drug is given; usually three-fourths of a grain of ephedrine hydrochloride. We believe it is important to give the drug one-half hour before operation for the best results. Should the pressure be above 130 mm., no drug is given at this time.

When the patient is brought to the operating theater she is placed on her side, on a table upon which there is a special mattress designed by Dr. Lemmon.

Under aseptic precautions, the initial skin wheal is made with procaine, between the first and second, or second and third lumbar interspaces. A stainless steel safety needle is inserted into the subarachnoid space. With the needle in one of these interspaces, the drug will reach above the umbilicus and will produce the desired level of anesthesia with the minimum amount of dosage.

A 10 c.c. ampule of procaine in Ringer's solution is then opened and placed in the syringe. This is a 1.5 per cent solution of procaine containing 15 mg. per c.c. The syringe is then connected to the tube, which is filled with the solution to expel the air. The tube is then connected to the needle and the initial dose is given. The average initial dose is 15 mg.

The patient is then turned on her back and placed in a five-degree Trendelenburg position. The needle is then checked to determine whether it is still in the subarachnoid space. This is done by aspiration with the syringe. If no fluid is aspirated, the needle must be adjusted until there is a free return flow.

The length of time for the establishment of anesthesia is usually five to ten minutes, during which time the abdominal field is prepared and draped. If the level of anesthesia is not satisfactory, an additional 1 c.c. of procaine is given.

The blood pressure, pulse, and respirations are taken every five minutes during the operation.

The systolic pressure seldom drops more than 10 to 12 mm. and in many patients there is a drop of less than 10 mm. of mercury. If the systolic level reaches 90 mm. or less, three-fourths grain of ephedrine hydrochloride is given hypodermically and glucose in saline solution is given intravenously. Plasma should be available. If there is a persistent fall in blood pressure, the vasopressor drug is given intravenously.

If the anesthesia begins to wear off or the patient complains of discomfort at any time during the operation, additional doses of procaine can be given, usually in 0.5 to 1 c.c. dosage, which represents 7.5 to 15 mg. of the drug.

During the past year and a half we have been starting a continuous drip solution of Pentothal sodium, 0.5 per cent, at the rate of 45 drops per minute when the operation begins. This quiets the patient but does not put her to sleep. Following the extraction of the child it is increased to about 90 drops a minute. This allows the patient to hear her baby cry and to know that he is all right. On increasing the dose of Pentothal she then sleeps through the

TABLE III. CESAREAN SECTIONS FROM JAN. 1, 1941, TO JUNE 1, 1948

Performed under continuous spinal	1000
Performed under continuous caudal	162
Performed under general anesthetics	174
Performed under local infiltration	5
Performed under single injection spinal	37

When we first instituted the use of fractional spinal we decided to confine ourselves to the use of only three drugs; not because we thought these three were more satisfactory than others on the market but rather in order to simplify and better control our study of this series. In some of our experimental work with caudal we found that procaine in Ringer's solution seemed to have a more lasting effect than either Metycaine or procaine hydrochloride.* Table IV shows the number of patients to whom these drugs were administered for spinal anesthesia.

TABLE IV. DRUGS USED IN CONTINUOUS SPINAL ANESTHESIA CESAREAN SECTIONS

Metycaine, 1.5%	692
Procaine in Ringer's Solution	194
Procaine hydrochloride	114

TABLE V. AVERAGE DROP OF SYSTOLIC BLOOD PRESSURE IN 1,000 CASES OF CESAREAN SECTION UNDER CONTINUAL SPINAL ANESTHESIA

Metycaine (692 cases)	13.0 mm. of mercury
Procaine in Ringer's Sol. (194 cases)	1.5 mm. of mercury
Procaine hydrochloride (114 cases)	11.5 mm. of mercury

One of the most frequent complications that occurred when we were using single-dose spinal years ago was the development of marked hypotension. During our early use of continuous caudal and before we knew how to combat this condition, we noticed that the unborn child was definitely affected, as evidenced by the tumultuous movements which occurred in the uterus during the period of hypotension. We are not condemning single shot spinal because if it is given properly this complication can be avoided. Since the technique of administration has been refined and the drugs used today are less toxic, most anesthetists do not fear hypotension. It was our belief that if the patient were given small doses to begin with and then they were gradually increased until a satisfactory level of anesthesia had been obtained, there would be less opportunity for complications to develop. In most patients, any serious complication will usually develop within a period of five or ten minutes after the initial injection. Although it is contended that neurogenic fixation of these drugs occurs within from six to twenty minutes after they are administered, Hingson *et al.*,¹ in studying 100 patients who had fractional spinal anesthesia, removed several

TABLE VI. AVERAGE DOSAGE OF DRUGS USED

All drugs	65.9 mg.
Metycaine	58.01 mg.
Procaine in Ringer's solution	71.4 mg.
Procaine hydrochloride	108.9 mg.
Number of cesarean sections done with 15 to 30 mg. of anesthetic drug	71

*At our request, the Abbott Laboratory very kindly made up for us some procaine in Ringer's solution to be used in our study.

periences in previous vaginal deliveries or because the patient was in the late third or early fourth decade of life, and particularly where the fulfillment of the desire for offspring was of paramount importance. We performed nine cesareans because the mothers were Rh-negative and the fathers were Rh-positive, with change in the titers. At the present time we are of the opinion that if these patients had been allowed to go to full term and had been delivered vaginally, these babies would have been normal children and we would not have had to deal with the problem of prematurity. There were two patients with leucemia; one who comes under the classification of previous section, having had one section performed in another institution because of cephalopelvic disproportion, and one who had made several ineffectual attempts at going into labor and because of her rapid downhill progress it was thought best to terminate the pregnancy in this manner. As will be seen by this table, there were more than 1,000 indications for cesarean section. This is explained by the fact that in several instances there was more than one indication for the operation.

TABLE IX. NUMBER OF FAILURES UNDER CONTINUOUS SPINAL ANESTHESIA: 27

Technical failures	10
Level not sufficiently high to proceed with operation, supplemental anesthetic necessary	17

Among the patients who were scheduled for operation under this technique, there were 27 failures; ten were technical failures as the anesthetist was unable to insert the needle properly, and in seventeen a satisfactory level could not be obtained in spite of increased dosage of the anesthetic drug. In five of these seventeen patients, the needle had been dislodged in moving the patient and this was not recognized until after the abdominal incision had been made. Further instillation of the drug was not possible and a supplemental inhalation anesthetic became necessary.

The maternal mortality in this series included one case of leucemia, with the death occurring 12 days after operation. This patient had a rapidly progressing acute leucemia and death was due to this disease. Autopsy showed a perfectly healed uterine scar. Refinement of technique and emphasis on the choice of anesthetic, and the choice of the type of operation performed in these patients, will unquestionably give rise to the reporting of other large series with no maternal mortality. Waters² reports no deaths in the last 650 cases at the Margaret Hague Maternity. He ascribes the low cesarean mortality largely to the selection of the operation. In this we concur. The decrease also may be attributed to the development and use of the various antibiotic drugs but we are strongly of the opinion that it is a combination of choice of anesthesia and type of operation which is most important.

TABLE X. FETAL MORTALITY

1. Stillborn	14
a. Abruptio placentae	9
b. Malpresentation	4
c. Premature (7 months) death	1
Operation, twisted ovarian cyst	
2. Neonatal	33
a. Prematurity	23
b. Cerebral hemorrhage	1
c. Congenital heart disease	4
d. Rh, erythroblastosis	3
e. Hydrocephalus and spina bifida	1
f. Congenital atresia of esophagus	1
Total fetal deaths	47
Uncorrected fetal mortality	4.7%

remainder of the operation but is usually awake when she leaves the operating table. An oxytocic drug, usually a preparation of Ergotrate, is given as a routine procedure and the patient, while still on the table, is also given one-fourth grain of morphine. Upon her return to her room, the patient is placed flat in bed and allowed to have fluids and soft food on the day of operation.

TABLE VII. TYPE CESAREAN SECTION

Low classical	479
Low flap	452
Extraperitoneal	53
Cesarean hysterectomy	16

Table VII shows the various types of cesarean performed upon these 1,000 patients. The incidence of low section has increased 127 per cent in the last ten years. We do not do the low section as a routine procedure, particularly when the operation is elective and when a previous cesarean section has been performed, or when sterilization is to be carried out. Our results with the extraperitoneal type of operation have been extremely satisfactory and we believe this is the procedure of choice in potentially infected cases. We do not believe that cesarean hysterectomy is preferable to the extraperitoneal operation in these infected cases. Neither do we feel that hysterectomy is necessary in order to produce an effective sterilization. The cesarean hysterectomies performed in this series were upon patients who had complicating myomatous tumors.

TABLE VIII. INDICATIONS FOR CESAREAN SECTION

1. Cephalopelvic disproportion	382
2. Pelvic tumors	30
3. Abruptio placentae	32
4. Placenta previa	62
5. Toxemia of pregnancy	42
6. Cardiac disease	18
7. Pulmonary disease	5
8. Kidney disease	4
9. Elderly nullipara	25
10. Recent or extensive vaginal plastic	40
	a. Previous section 268
	b. Overvaluable baby 14
	c. Difficult previous delivery 9
11. Elective cesarean sections	d. Uterine anomalies 5
	e. Prolapse of cord 6
	f. Diabetes mellitus 2
	g. Malpresentation 40
	h. Rh syndrome 9
12. Dystocia syndrome	40
13. Prolapsed colostomy with obstruction	1
14. Uterine inertia	5
15. Leucemia	1

Table VIII shows the indications for cesarean section in this series. This classification of indications was adopted by our staff several years ago. All of our cases of cephalopelvic disproportion are x-rayed and the films are discussed by some member of both departments. Although we have increased the number of cesareans performed in abruptio and placenta previa, we do not believe that all of these patients should be delivered by this method. However, where there is any doubt, we perform a cesarean section rather than employ conservative treatment. Our incidence of cesarean section in cardiac disease has decreased considerably since the advent of the various forms of conduction anesthesia for vaginal delivery. In this group, 268 patients had had previous cesarean section. There were fourteen elective operations performed because of disastrous ex-

to be fat. About one week before entry in the hospital, she developed a pain in the left lower quadrant. She had no nausea, vomiting, urinary symptoms, nor bowel disturbance. She went to bed because of the pain and after one week she felt well again. She complained of considerable fatigue during this time.

Physical Examination.—Temperature, pulse, respiration, and blood pressure were normal. She had a normal feminine habitus (Fig. 1). There was mild hirsutism of the face, especially of the upper lip and chin (Fig. 2). No chest hair was present. The breasts were small.

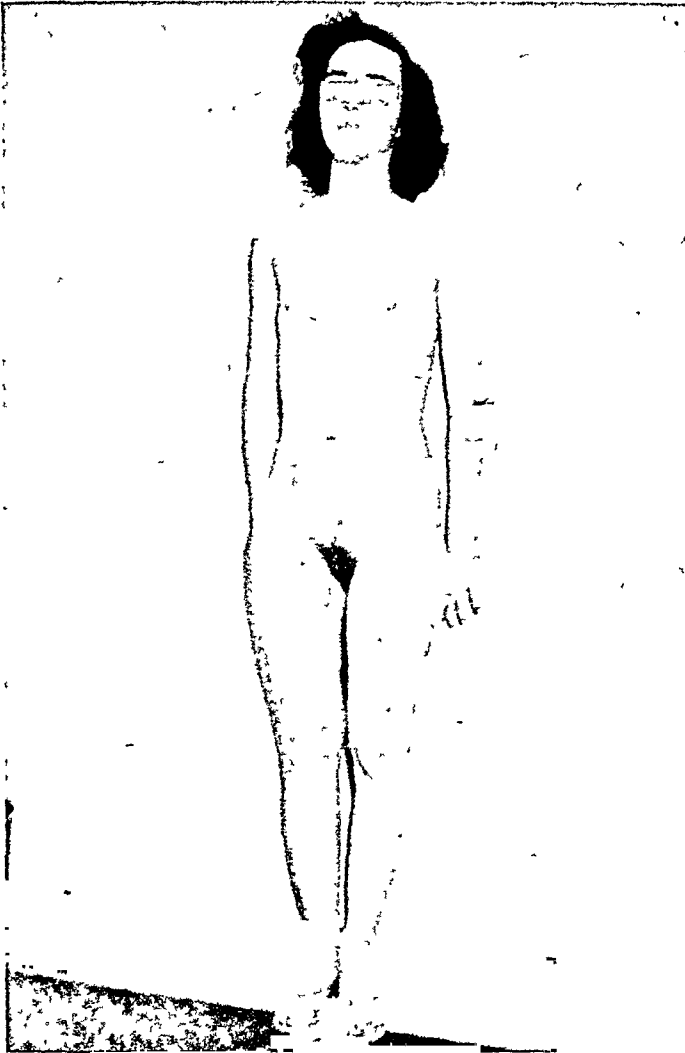


Fig. 1.—Photograph shows normal feminine habitus.

The pubic hair was heavy and dark with mild tendency toward masculine distribution. Heavy growth of hair on the lower extremities was noted. The abdomen was enlarged to the size of a six months' pregnancy. On palpation, a mass could be felt arising from the pelvis which gave one the impression of encysted fluid. A questionable fluid wave was present. No shifting dullness was noted. The abdomen was tympanitic above the mass and dull over it. No sounds were heard over the mass with the stethoscope. No other masses were felt. The liver, kidneys, and spleen were not palpable. Pelvic examination revealed heavy pubic hair, normal external genitals, with the exception of a markedly hypertrophied clitoris (Fig. 3). The hymen was intact. The vagina and cervix were normal to palpation. The

Table X shows the fetal mortality. This was uncorrected and several of these babies were quite premature. In 986 babies born alive in this series, only one required actual resuscitation other than clearing out the upper respiratory passages. This occurred in a 6½ months' premature infant born to a patient who had a premature separation of the placenta. This baby died five hours after delivery but weighed only one pound, twelve ounces.

TABLE XI. MORBIDITY

Endometritis	77
Pyelocystitis	34
Mastitis	13
Thrombophlebitis	10
Intercurrent infection	13
Dehydration	2
Morbidity—cause unknown	12
Wound infection	21
Atelectasis	1
Postoperative reaction	26
Transfusion reaction	4
Drug sensitivity	1
Total	214 — 21.4%

Table XI shows a 21.4 per cent morbidity, based on the standard of an elevation of temperature of 100.4° F. on any two days during the first ten days but excluding the first 24 hours after delivery or operation.

TABLE XII

<i>Number of Patients Requiring:</i>	
1. Intravenous glucose	31
2. Supplemental vasopressor drugs	238
3. Blood transfusion	9
<i>Distention:</i>	
Mild-moderate	32
Wangensteen drainage	4
<i>Headache:</i> Postspinal headache	16
<i>Neurologic Complications</i>	0

Table XII is interesting from several standpoints. In this series we did not routinely give intravenous fluids except for a definite indication. Two hundred thirty-eight of these patients had developed sufficient hypotension to warrant the giving of supplemental vasopressor drugs. Nine required blood transfusions and were all patients with serious hemorrhage from abruptio or placenta previa. We have been particularly impressed by the small number of patients who suffered from distention following cesarean section. It was necessary to institute Wangenstein drainage in only four patients in this series of 1,000. Although the resident staff had been instructed to write on the record any incident of headache, there were only 16 postspinal headaches recorded. This figure we believe to be incorrect. We are sure that there were several more but the headaches were not of sufficient severity to be brought to the attention of the visiting staff. In reviewing our impressions concerning spinal headache occurring in conjunction with the single-dose spinal and with the fractional method, we feel that there has been a comparatively small number in this series. We hesitate to consider the possibility that the fractional method is responsible for this decrease in incidence of postspinal headache since we do not have accurate statistical data to substantiate our belief. We did not become spinal headache conscious until after we had used this method for two or three years. This postoperative complication, as we have seen it, is a troublesome one but as a rule is relieved almost immediately by the application of a wasp girdle or in-

section of an inflated rubber bladder under a tight binder. We have seen one or two instances in our gynecological service where the headache has been persistent over a period of several days and nothing seemed to relieve the patient except keeping her perfectly flat. At the present time we are delivering a large number of our obstetrical patients by the use of saddle block or terminal one-dose spinal and are attempting in this series to obtain much more accurate data concerning the incidence of headaches in these patients. In this series there were no neurological complications although there have been reports of serious complications in the nervous system following use of spinal. We believe that if the technique is meticulously carried out these complications will be reduced to a minimum and we feel very strongly that the use of either fractional or single-dose spinal anesthesia should not be condemned because these complications occasionally occur.

Summary

We believe that our experience in studying this rather large series of patients, using the above outlined technique, has shown us many advantages of this method. The safety of continuous spinal anesthesia lies mainly in adhering to a rigid technique and we believe that the use of a smaller dose of the drug is an additional safeguard to the patient. This method also permits more controllability. The ease of administration allows it to be given by many different individuals, although we do not feel that a patient who has a spinal anesthetic of any sort should be supervised by anyone other than a trained anesthetist who has had experience in the use of all forms of conduction anesthesia. The excellent contraction of the uterine musculature with a minimal amount of blood loss is outstanding. The absence of narcosis in the baby offers one of the greatest advantages. This is particularly true where the baby is premature, as most of these will establish respiratory efforts almost before they are extracted from the uterus. Because of this fact, care should be taken to aspirate as quickly as possible the amniotic fluid which might be in the infant's mouth. Relaxation of the abdominal wall enables the operator to perform the operation with facility and dispatch. This type of anesthesia causes no disturbance of previously existing pathology in the respiratory, circulatory, or genitourinary system of the mother as the drugs used are low in toxicity and a minimal dosage is employed. The postoperative convalescence of these patients is marked by extreme comfort as compared with those given a general anesthetic and the postoperative complications such as distention and vomiting are kept at a minimum. We do not feel that the postoperative complication of spinal headache in this series occurred frequently enough to warrant criticism of the method used.

Conclusions

Our analysis of 1,000 women delivered by cesarean section under fractional spinal anesthesia has demonstrated to us the following facts:

That, in addition to many other improvements in operative technique of which we are cognizant, fractional spinal anesthesia is definitely a safeguard to the operation of cesarean section.

That we should not condemn single-dose spinal anesthesia, as we know that, in proper hands, complications which may result from the large single-dose injection can be avoided. However, we do feel that a word of caution should be added when spinal is given by that method.

That we prefer the fractional spinal to the single-dose method because of its safety and the many advantages of administration which it affords.

That in order to bring our maternal mortality to an irreducible minimum we must surround all of our patients with every safeguard available. In cesarean section we believe that fractional spinal anesthesia is another safeguard.

807 SPRUCE STREET, PHILADELPHIA 7

255 SOUTH 17TH STREET, PHILADELPHIA 3

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Discussion

DR. S. A. COSGROVE, Jersey City, N. J.—This presentation is of special interest because it exhibits the qualities which make for a great clinic, that is to say, the restless search for constant betterment in method and in concept. There is perhaps no one who can better appreciate the extent of this shift of base over the years in relation to anesthesia, and I very sincerely rejoice with the authors of the paper on the extensive and discriminating work which they have done with a variety of forms of lower-neuron anesthesia and analgesia, and their ready acceptance of those techniques which from time to time appear to merit their confidence most. The decrease in general maternal mortality at the Philadelphia Lying-In is outstanding, and the very low postcesarean death rate is remarkable and commendable. The authors report an incidence of cesarean section of 7.2 per cent in a service which represents 65 per cent of private cases. It is hardly necessary for them to defend this incidence so extensively, because it is the same excuse we all use to justify a higher incidence of section in our private work than we permit our Residents to use in the Ward Service cases. The very decided shift toward the lower segment type of operation, the moderately extensive use of extraperitoneal section, and the practice of reserving cesarean hysterectomy for other indications than uterine infection are all salutary trends. About the only detail in the whole paper with which I do not concur is the plan always to do repeat sections on women who have had any kind of section, for any kind of an indication previously, in order to eliminate the "stress and strain on the accoucheur during these labors." I am interested that the Philadelphia experience has shown that for this work procaine is the most acceptable drug. I am also interested in the suggestion that this is best administered in Ringer's solution, although we have not personally had experience with this detail of technique.

For a considerable time we have been starting a continuous drip of glucose-sodium chloride solution before any spinal anesthesia is started. Not only does this appear to have the advantage of stabilizing the circulatory status, but it pre-establishes a channel through which vasopressor drugs, oxytocics, supplemental anesthetics such as Pentothal, plasma, and blood, may all be readily used as they may be indicated.

Finally, I want to stand shoulder to shoulder with Drs. Lull and Ullery in their advocacy of lower-neuron anesthesia for all the operations of obstetrics, in the interest of both the mother and the fetus. Neither I nor they care to dictate to anyone else the precise form of such anesthesia employed. Nor do we have the slightest interest whatever in forcing our own opinions and practices on others. I do hope, however, that the significance of this splendid presentation, with every essential of which I thoroughly agree, will not be lost on those who have so far failed to appreciate the advantages of these forms of anesthesia over those which so needlessly, and frequently so harmfully, obtund the higher cerebral centers.

DR. M. PIERCE RUCKER, Richmond, Va.—It has not been so very long when to have delivered 1,000 cases per vaginam with but a single death would have been considered a noteworthy feat. Drs. Lull and Ullery report a thousand cesarean sections with one maternal death and that from leucemia 12 days after delivery. Their fetal mortality, 4.7 per cent, also deserves comment. Furthermore, their series is unique in that the thousand sections were done under a single type of anesthesia.

There is one disturbing aspect of this report. It is so good that it will certainly stimulate others on the same scale. This will mean in many instances widening the indications for cesarean section in order to get numbers. For instance, our incidence of sections is less than 0.7 per cent. In order to get a thousand cases we will have to deliver 142,857 women or else widen our present indications. I wish to add one more indication to Dr. Lull's list and that is inadequate abdominal wall. In June of this year a multipara was admitted to the Sheltering Arms Hospital with a tremendous postoperative abdominal hernia and cellulitis of the abdominal wall. Her story was that 15 months previously an appendectomy had been done through a midline incision. When she began to get big with the present pregnancy the scar became black and soon the adjacent abdominal wall became inflamed. She was treated with compresses of normal salt solution and with penicillin and the cellulitis disappeared. She returned to the hospital in August. The whole uterus was in the hernial sac, and the overlying abdominal wall was very thin. The scar was still black and had begun to widen. Her temperature and pulse were normal. She was again treated with penicillin and compresses and on August 26 Dr. Edwin Rucker did a section under continuous spinal anesthesia, using procaine dissolved in spinal fluid. He made a lateral incision and after doing a low flap operation removed the redundant abdominal wall and repaired the hernia. The patient was out of bed the next day. She had an afebrile postoperative course and she and her baby were discharged in good condition.

There is another aspect of Dr. Lull's paper that fills me with envy and that is his ability to predict a prolapsed cord so as to plan an elective cesarean section. He had six such cases. If he will teach me how to do that, I will add that to my indications. Otherwise his indications for section are in the main the ones we have followed. We have not performed a section for heart disease nor have we done one because the patient had had a vaginal plastic operation. I believe we do fewer proportionately for placenta previa and the toxemias of pregnancy. On the other hand, we did in our small series actually more for diabetes mellitus than did Drs. Lull and Ullery. Most of our cases of diabetes are referred to us and are treated by a specialist in that disease. In some of them the gonadotropic hormones get out of control at about the 36th week, and in such cases we usually do a section.

In regard to the type of operation, our series since 1941, includes fourteen classical cesarean sections, thirty-one low-flap operations, and five extraperitoneal sections. One was done under nitrous oxide-ether, six under ether, eight under ethelene, three under intravenous Pentothal, two under local, ten under local with Pentothal for the uterine incision, and nineteen under continuous spinal anesthesia. One of our patients was operated upon in a neighboring city for premature separation of the placenta, and my notes in her case do not show what anesthesia was used. There were no maternal deaths. We had eight fetal deaths, including a nonviable 6 months' baby whose mother had advancing tuberculosis and another about the same age whose mother was pre-eclamptic.

I was interested to note that the authors noted no neurologic complications. None of our cases in which a section was done had such complications, but two patients who had been given continuous spinal anesthesia for vaginal delivery, developed spinal meningitis afterwards. Both developed the meningitis after their postpartum examination at the fourth week. Both were extremely sick, but fortunately recovered. In neither case could bacteria be demonstrated by smear or culture, and in neither case could the internist ascribe a cause for the disease. This occurred during the war when discussion of infectious hepatitis had made us virus-minded. If we assume that the spinal injection were the cause, the prolonged incubation period and the sterile cultures would suggest a virus infection. A 1 per cent procaine solution in normal saline was used in each case. The solution was sterilized in the

hospital by boiling and the tubing, needles, syringes, etc., were autoclaved. The skin was prepared with tincture of iodine and alcohol and the anesthetist used sterile rubber gloves. Since this occurrence, we have not used continuous spinal anesthesia for vaginal delivery, but I still think it the most satisfactory anesthetic for a cesarean section.

DR. LULL (Closing).—May I thank both Dr. Cosgrove and Dr. Rucker for their very kind discussion of this presentation. I was particularly anxious to have both of them discuss this paper because of their wide experience in the use of spinal anesthesia. We all look to Dr. Cosgrove as being one of the outstanding pioneers in this work. For many years I disagreed with Dr. Cosgrove concerning the use of spinal anesthesia, particularly in cesarean section cases. I now have reversed my opinion and agree most heartily with him and I believe the statistics as borne out in this presentation will show that it is probably the safest anesthetic both for the mother and for the child. Both Dr. Ullery, my associate, and I feel that the use of fractional spinal is another safeguard to the woman undergoing an operation for abdominal delivery. When we started this work in 1941 we felt that we did not want to make any definite report on our findings until we had had a sufficiently large group of patients and we therefore set arbitrarily on the number as being one thousand. As our series progressed we found that the many factors which were so satisfactory, such as small amount of blood loss, the baby being in such good condition; and the quick recovery of the mother, were so pronounced that it is only occasionally that we resort to any other type of anesthesia.

ELDERLY PRIMIGRAVID WOMEN*

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AMONG primigravid women the problem of age and aging in relation to pregnancy and parturition is as old as the practice of obstetrics. Naturally, therefore, literature concerning this subject extends back to the ancients. Differences of opinion come to light most sharply for the first time in the attitude of Mauriceau and Madame Lachapelle. The former found that the labors of elderly primigravid women were longer and more severe than those of other primigravid women and that these patients more frequently suffered from eclampsia. He stated that the weight of the children was greater than normal and that the mortality rate among them was greater. Lachapelle on the contrary maintained an optimistic attitude and remarked that "no doubt one often observes a slow and painful labor in the older primigravidas, but is it not the same in all ages?" She ventured the opinion that the proportion will be about equal.

A similar division of opinion is somewhat apparent in the modern literature. To those interested in the subject we recommend the thesis of Lundh published in 1926 as an exhaustive, interesting, and instructive exposition. His material concerned 7,000 primiparas between the ages of 13 and 47 years. Briefly his conclusions indicated a history of delayed onset of menstruation among elderly primiparas; an increase in the incidence of toxemia; the highest incidence of premature labor among the younger group; an optimum for the duration of labor around the twenty-second year of life with a gradual increase after the age of 25 years, coinciding with an increased inefficiency of the uterus and rigidity of the soft parts, and with an increase in the incidence of operative delivery and damage to soft tissue. In the older group of parturients he found a prolongation of the third stage of labor with an increase of necessary intervention at that time. He reported no change in the weight, bodily length, or circumference of the head of the infants and no change in the ratio of sex among them. There was an increase of the number of twin pregnancies. He noted a considerable increase of infant morbidity and mortality rates.

A few articles have appeared in the past ten years on this subject but the latest discussion before this society was by Quigley in 1930. The matter attracted our attention several months ago when a primigravid woman 45 years of age passed through a pregnancy and parturition with the facility of a woman of 25 years, giving evidence perhaps that her physiologic age was more to be considered than her calendar age.

*Read at the Fifty-Ninth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Virginia, September 9 to 11, 1918.

A uniform definition for the elderly primigravid woman does not seem to exist. Definitions are based on the actual age of the patient and vary from those more than 30 years of age to those more than 35 years of age and in one instance to those more than 38 years of age. Accordingly, we selected data on three groups of primigravid patients from the records of the Mayo Clinic for comparative study: 250 who were 35 years of age or older, 516 aged 30 through 34 years and 792 who were less than 30 years of age. Those data that seemed pertinent and which offer bases for comparison are enumerated and discussed herein. A number of patients came to us for emergency care having had prenatal care elsewhere or none at all. In some cases attempts had been made to deliver the infant before the mother was admitted to our service, but except for an occasional comment these patients are not specially designated in the paper. As might be expected in any group of 1,558 gravid women numerous medical and surgical complications occurred, many only once or twice, and there seems to be no reason to catalogue all of them in this paper.

Among the medical and surgical complications certain items evidence an expected trend. In the group more than 30 years of age significant disease of the thyroid was present eleven times. Ten patients were found to have adenomatous goiter and one had exophthalmic goiter. Three of these patients underwent operation during pregnancy. Of the 250 patients 35 years of age or older four had carcinoma. One patient had undergone radical mastectomy previous to an uneventful pregnancy and parturition. She died five years later as the result of an accident. One patient was found to have carcinoma of the breast when she was in the seventh month of gestation. Radical mastectomy was performed and the infant was later delivered by cesarean section. The patient died three years later of carcinoma. Another patient underwent operation for adenocarcinoma of the rectum early in pregnancy and subsequently the infant was delivered by cesarean section. In one patient carcinoma in situ of the uterine cervix was discovered at the time of the postpartum examination and was treated by total abdominal hysterectomy.

The older women more often entered on pregnancy with an elevation of blood pressure than the younger women. At less than 30 years of age pre-existing hypertension was found in only 1 per cent of patients; from 30 through 34 years of age it was found in 3.9 per cent, while after the age of 35 years 11.6 per cent of women were found to have an increase of blood pressure either before pregnancy occurred or very early in pregnancy. Thus, as would be expected, the vascular system becomes more vulnerable with age. Many women who have hypertension pass through pregnancy without incident if renal function remains normal but if toxemia becomes superimposed on a pre-existing hypertension a serious situation exists.

The incidence of toxemia of pregnancy increased with age. Those patients less than 30 years of age experienced it in 10.7 per cent of cases; from 30 through 34 years of age toxemia was a complication in 13.7 per cent, while of those 35 years of age or older 18.4 per cent suffered from toxemia. These patients having toxemia include all those in whom pre-eclampsia in its various degrees of severity developed. Two patients who had eclampsia, both in the two older groups, were admitted for emergency treatment. Our over-all incidence of toxemia is approximately 6 per cent but in this sample of 792 women less than 30 years of age from three separate years for comparison the incidence of toxemia was 10.7 per cent.

The behavior of the uterus and cervix during labor revealed some differences. Among those patients experiencing vaginal delivery were a number who were considered to have uterine inertia, either primary or secondary,

on whom Dührssen's incisions were performed or in whom it became necessary to complete the last 2 or 3 cm. of dilatation manually. Thus in those 792 patients less than 30 years of age uterine inertia was diagnosed 14 times, Dührssen's incisions were made in 3 cases and the dilatation of the cervix was completed manually in 2 cases, making a total of 19 cases (2.4 per cent) in which the behavior of the uterus and cervix constituted a complication of labor. Among the 516 patients from 30 through 34 years of age, uterine inertia occurred fifteen times, Dührssen's incisions were performed in six cases and manual completion of cervical dilatation was performed in three cases, a total of twenty-four cases (4.6 per cent). When the patient was 35 years of age or older, uterine inertia was considered present in six of 250 patients, Dührssen's incisions were made in four and in six manual completion of cervical dilatation was performed, a total of sixteen (6.4 per cent). These numbers are small but they indicate a trend.

One may also consider the efficiency of the uterus as reflected by two other conditions. Errors of rotation of the occiput were more frequently encountered among older than among younger women. Among the 792 less than 30 years of age 33 errors (4.2 per cent) of anterior rotation that necessitated correction were present, from 30 through 34 years of age this occurred in 10.4 per cent and it occurred in 27 (10.8 per cent) of those patients 35 years of age or older. These errors or failures of normal rotation were corrected by various means. The factor of inefficient expulsive effort with perhaps the additional one of resistant soft parts is further reflected by the increase of necessary intervention at a higher plane in the pelvis among women in the older age group. Thus, in the group of 792 women less than 30 years of age, a midforceps operation was performed in 10 cases (1.3 per cent); in the 516 women from 30 through 34 years of age, 38 (7.4 per cent) required this procedure, and when the patient was 35 years of age or older, 30 of 250 (12.0 per cent) underwent the midforceps operation.

Induction of labor by castor oil and Pitocin, rupture of the membranes, or insertion of a hydrostatic bag occurred more frequently among the older age group than among those who were younger. At ages less than 30 years induction of labor was performed in 34 (4.3 per cent) of 792 patients; from 30 through 34 years of age among 516 patients, 56 (10.8 per cent) underwent induction of labor and in those patients 35 years or older 33 (13.2 per cent) had labor induced. These inductions were performed most frequently in the presence of toxemia of pregnancy.

The spread of occurrence of premature separation of the normally implanted placenta and placenta previa did not seem significant among these patients. In our experience at the clinic placenta previa has occurred in primigravidas in 19 per cent and in multiparas in 81 per cent of all cases of placenta previa, so that the number of women among these groups who had placenta previa was too small to bear analysis. The incidence of manual removal of the placenta, postpartum hemorrhage, and postpartum insertion of an intrauterine pack was actually less in the older than in the younger women but the totals are too small to merit comparison.

Premature rupture of the membranes occurred in 53 (21.2 per cent) of the 250 women 35 years of age or older compared to a general average of 12 per cent in the younger groups. Contracted pelvis was found in 41 (16.4 per cent) of 250 women 35 years of age or older and in 56 (10.8 per cent) of the 516 women aged 30 through 34 years. This difference is probably not significant.

As would be expected, the incidence and significance of myomas of the uterus increased with age. Among the 792 women less than 30 years of age myomas were noted only 15 times (1.9 per cent) but in 3 of these patients

myomectomy was performed during pregnancy. In only 1 patient in this group did the presence of myomas enter into the indications for cesarean section. In the remaining 12 of these 15 patients the myomas had no significant effect on pregnancy or parturition.

Among the 516 women 30 through 34 years of age, 39 (7.5 per cent) were found to have demonstrable myomas in the uterus. Twenty-one of these 39 patients did not experience any complications of pregnancy, parturition, or puerperium that could be attributed to the myomas. The remaining 18 of the 39 experienced some complication such as myomectomy, postpartum hemorrhage, adherent placenta, or degeneration of the myomas, or underwent cesarean section.

When the patients were 35 years of age or older, 42 (16.8 per cent) of these 250 women gave evidence of significant myomas in the uterus. In 30 of these patients no serious complication could be attributed to the myomas. In 12 patients, however, various complicating factors arose such as were mentioned previously and in 2 patients cesarean hysterectomy was performed.

Table I reveals the methods of delivery among the three groups of patients. It is to be remembered that these patients cover a period from 1924 through 1945 and therefore represent a period of considerable change in obstetric practice. For example, the high forceps operation has ceased to be used but in earlier days it was occasionally the only alternative in certain cases. We have always restricted the indications for podalic version and extraction, as is evident. Breech extraction was performed in about the same percentage in each group, indicating that, unless definite cephalopelvic disproportion exists, infants can be born by breech in primigravid women in all age groups.

TABLE I. NUMBER OF DELIVERIES AMONG PRIMIGRAVID WOMEN BY METHOD OF DELIVERY

METHOD OF DELIVERY	AGE OF WOMEN, YEARS					
	LESS THAN 30		30 THROUGH 34		35 OR OLDER	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Spontaneous	423	53.5	210	40.6	78	31.2
Low or outlet forceps	303	38.2	209	40.5	91	36.4
Midforceps	10	1.3	38	7.4	30	12.0
High forceps	0		2	0.4	1	0.4
Version and extraction	0		4	0.8	2	0.8
Breech extraction	32	4.0	34	6.6	13	5.2
Cesarean section	23	2.9	16	3.1	32	12.8
Craniotomy	1	0.1	3	0.6	3	1.2
Total	792	100.0	516	100.0	250	100.0

Cesarean section deserves further comment. We have always tried to individualize all treatment in obstetrics and have applied this principle to the use of the cesarean operation as well. The incidence of the operation among those women less than 30 years of age is 2.9 per cent; it increases to 3.1 per cent when the patient is from 30 through 34 years of age and rises sharply to 12.8 per cent among the patients 35 years of age or older. Our over-all incidence of cesarean section since 1934 is 3.5 per cent. It will be noted that the number of indications per operation also increases with age and that the type of indication changes (Table II). It is our policy to employ a test of labor when the character of the pelvic contraction is suitable for this procedure and this was carried out in six of the patients 35 years of age or older, five resulting in cesarean section and one in delivery through the vagina. Nine of the sixteen cesarean sections performed in the group from

30 through 34 years of age were preceded by a test of labor. Among women 35 years of age or older and more frequently when more than 40 years of age, the factors of number of years of marriage, lessened remaining years for reproduction, associated disease of the uterus, such as myomas, complicating vascular disease with or without toxemia, and coexisting or previous carcinoma will weight one's judgment and emphasize the factor of evidence of cephalopelvic disproportion as an indication for cesarean section.

TABLE II. INDICATIONS FOR CESAREAN SECTION IN PRIMIGRAVID WOMEN ACCORDING TO AGE

INDICATIONS	AGE OF WOMEN, YEARS		
	LESS THAN 30 (792 WOMEN)	30 THROUGH 34 (516 WOMEN)	35 OR OLDER (250 WOMEN)
Cephalopelvic disproportion	13	7	15
Breech presentation	3	0	4
Placenta previa	0	1	3
Myomas	1	6	11
Malposition	1	5	1
Toxemia	4	0	4
Vaginal atresia	0	0	1
Ovarian cyst	1	0	1
Diabetes	1	3	0
Brain tumor	1	0	0
Cesarean hysterectomy	0	0	3
Heart disease	0	2	0
Previous infertility	1	0	1
Radical resection of breast for carcinoma	0	0	1
Adenocarcinoma, rectum	0	0	1
Total	26	24	46
Operations	23 (2.9 per cent)	16 (3.1 per cent)	32 (12.8 per cent)

Naturally, the number of patients having significant myomas increases with age, as mentioned previously, and, though myomas were not usually the sole reason for section unless they produced obstruction to the birth canal, they were often an added reason for the operation. Cesarean hysterectomy was performed twice because of myomas and once because of a couvelaire uterus associated with hemorrhage into the broad ligament.

Toxemia alone, except in an occasional instance of fulminating toxemia that does not respond to treatment, particularly when the cervix is not ripe, is rarely considered an indication for section at the clinic. This condition became the indication or one of the indications in 8 of the total of 71 cesarean operations in all three groups.

The remainder of the indications need no comment. It is to be noted that in the older age groups multiple indications were frequently present. The only maternal death in all groups was that of a primigravida aged 43 years on whom a classic cesarean section was performed in 1933 for central placenta previa and who died on the third postoperative day, the diagnosis being peritonitis and paralytic ileus. No necropsy was obtained.

Six reports concerning elderly primigravidas which appeared between 1931 and 1944 were taken at random. The fetal mortality rate averaged 6.1 per cent. The incidence of cesarean section averaged about 14 per cent, though this average perhaps is not truly representative, for there was great variation of the incidence. The maternal mortality rates after cesarean section likewise differed greatly. The six reports listed no deaths in one group of 31 patients² who underwent cesarean section, no deaths in 35 patients,⁸

corpus could not be felt but the lower pole of a mass filling the cul-de-sac and extending above the umbilicus was noted. Rectal examination confirmed vaginal palpation. Laboratory data: Urinalysis, negative; blood count: red blood cells 3,540,000, white blood cells 8,050, hemoglobin 11.9 Gm. Differential count was normal. There was slight hypochromasia of the



Fig. 2.—Hypertrichosis of upper lip, thick eyebrows, and recession of hair about forehead.

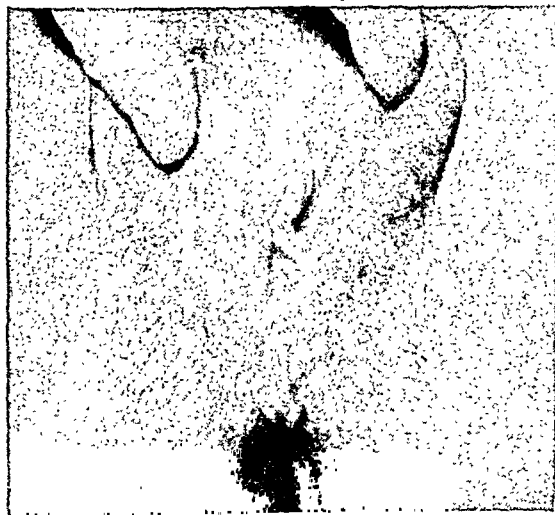


Fig. 3.—Hypertrophy of clitoris.

red blood cells. Platelets appeared adequate. Blood Kahn test negative. Her blood typing was group B, Rh positive. The diagnosis was ovarian cyst, probably a masculinizing tumor with possible torsion of the pedicle. Unfortunately, through a misunderstanding, urine was not collected preoperatively for determination of 17-ketosteroids.

Twenty-three of 251 infants born to the 250 women 35 years of age or older did not survive. Four of these deaths may be charged to operative vaginal delivery. In one instance forceps delivery failed in a case of cephalopelvic disproportion, the infant died in the second stage of labor and craniotomy was performed. A difficult midforceps operation resulted in a stillborn infant in one case. One infant died in the neonatal period after a low forceps delivery but postmortem examination was not permitted. The last of these four infants died during a version and extraction. In four infants hydrocephalus was present and in one anencephalus was found. Seven infants were macerated when born. Twins, weighing 1,000 Gm. each at birth, died during the neonatal period. One infant succumbed to erythroblastosis. Three infants died in the uterus but were born before maceration occurred and one infant died as a result of prolapse of the umbilical cord.

The expected date of confinement is not calculated without error. The obstetrician uses other criteria to estimate the ripeness of a pregnancy but to the patient the calculated date assumes much importance. We have checked this date against the fetal mortality rate. The results indicate that postmaturity calculated on this basis assumed no importance in the fetal mortality rate but that prematurity greatly influenced fetal salvage.

As has been indicated previously, those who have written concerning the elderly primigravid woman have approached the subject from variable points of view. This variation probably stems from the occurrence that motivated the construction of a paper on the subject. One develops a plan or philosophy of the practice of medicine generally and obstetrics in particular, partly from the experience of others but largely from the happenings in one's own experience. Whatever discussion we may state is so predicated. Perhaps impressions would be a better term and others may construe it variously.

Certain conditions may be expected to occur in any group of older women. Accordingly, adenomas of the thyroid, pre-existing hypertension, myomas of the uterus, and carcinomas were more evident among them than in a comparable younger group of obstetric patients.

We encountered more toxemias of the latter months of pregnancy among older primigravid women than among younger women and more frequently were forced to induce labor prematurely because of this condition. One of the components of these toxemias is arteriolar spasm, which must be more poorly borne by a patient who suffers from pre-existing hypertension. Needless to say, meticulous prenatal care and early recognition of, and adequate treatment for, these toxemias are of great importance.

The efficiency of behavior of the genital tract during parturition seems to us to decline with advancing years. Replacement of the musculature of the uterus by myomatous tissue probably plays a part as well as a diminution of the elasticity of the soft tissues of the pelvis. The increase of dysfunction of the uterus and cervix, the increase of failures of rotation of the occiput and the larger number of operative procedures at a higher level in the birth canal bespeak this lack of efficiency. Perhaps the larger percentage of patients experiencing premature rupture of the membranes belongs in this same category. There was an increase of the number of patients whose pelvic diameters were smaller than normal, as has been noted by others. This increase, though small, assumes added significance when related to the factors mentioned previously. All of these involve an increased risk to the mother. In competent hands this should be minimal but we know that maternal morbidity and mortality rates tend to increase as the incidence of operative delivery mounts.

Various reasons are given for the increased performance of cesarean section among these older women. One reason relates to the value of the infant

three deaths in thirteen cases,⁹ two deaths in eleven cases,¹ three deaths in 56 cases,³ and five deaths in 111 cases.⁴ This represents thirteen (5.1 per cent) deaths in 257 elderly primigravidas who underwent delivery by cesarean section, a figure higher than we had anticipated. The cases reported in these six groups of patients total 1,780. Cesarean section was performed in 257 cases, an incidence of 14 per cent. It must be remembered, however, that these reports concern long periods and many of these cesarean sections no doubt were performed before modern techniques and safeguards were available.

Our own instance of death after cesarean section occurred under these circumstances. If we consider all patients 30 years of age or older, this one death gives us an operative mortality rate of 2 per cent; if only those 35 years of age or older are included (this patient was 43 years of age), the mortality rate is 3.1 per cent. We have performed more than 400 consecutive cesarean sections since 1934 without a death. Certainly chemotherapy, antibiotics, the blood bank, low cervical and extraperitoneal cesarean section have contributed to this record.

One of the most significant items in this study concerns the fetal mortality rate. The figures shown in Table III are uncorrected. It is obvious that, if the intrauterine deaths alone were excluded, an appreciable alteration would be made. The fetal mortality rate was more than three times as great among infants born to mothers 35 years of age or older compared to those born to mothers less than 30 years of age. This increase seems to correlate with the increase in cases of toxemia and to relate also to the incidence of prematurity but in many instances the cause could not be accurately determined, particularly in premature macerated fetuses. Table III also reveals that the number of infants weighing less than 2,500 Gm. at birth increases very appreciably among the older group of patients. The 31 cases (12.4 per cent) in which the mother was 35 years of age or older are influenced by the increased incidence of induction of labor mentioned previously and by the intrauterine death of premature infants.

TABLE III. MORTALITY RATE OF INFANTS BORNE BY PRIMIGRAVID WOMEN ACCORDING TO AGE OF MOTHER, AND NUMBER OF INFANTS WEIGHING LESS THAN 2,500 GM. AT BIRTH

DEATH OF INFANT	AGE OF MOTHER, YEARS					
	LESS THAN 30 (792 WOMEN)		30 THROUGH 34 (516 WOMEN)		35 OR OLDER (250 WOMEN*)	
	INFANTS	PER CENT	INFANTS	PER CENT	INFANTS	PER CENT
Before onset of labor	8	1.0	16	3.1	14	5.6
During labor	8	1.0	5	1.0	4	1.6
Neonatal	6	0.8	5	1.0	5	2.0
Total	22	2.8	26	5.1	23	9.2
Infants less than 2,500 Gm. at birth	46	5.9	34	6.6	31	12.4

*One pair of twins, making 251 infants.

Analysis of the infant mortality rate in the two groups of older women reveals that, of the 516 children born to mothers aged from 30 through 34 years, 26 did not survive (Table III). None of these may be charged to the delivery. Three infants suffered from hydrocephalus and three from anencephalus. Twelve infants were macerated when stillborn but did not reveal gross defects. Two infants died before the onset of the second stage of labor, one in association with severe toxemia in the mother and in one case delivery had been attempted elsewhere and the infant was dead on admission to the hospital. One infant was stillborn at the time of cesarean section. Five infants died during the neonatal period, all weighing well under 2,500 Gm.

intervention at a higher level in the pelvis was more often necessary among older patients.

Cesarean section has an increased place in the delivery of infants among elderly primigravidas but the indications should be carefully considered and individualized. An incidence of 12.8 per cent for the performance of cesarean section seemed justified in this group of patients.

Prenatal care is now well standardized among well-trained obstetricians but these principles must be applied with increased care to elderly primigravidas, for they experience an increased incidence of toxemia.

In our experience the infant bears the major risk when pregnancy occurs in elderly primigravid women.

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Discussion

DR. JOHN H. MOORE, Grand Forks, North Dakota.—Dr. Randall's study of a group of obstetric patients, whom he designated as elderly primigravid women, has resulted in some interesting conclusions. My attitude is that of Madame La Chapelle, rather than that of Mauriceau. I am completely in accord with the statement of the essayist that "physiologic age was more to be considered than calendar age."

I was surprised to find Dr. Randall classifying 516 patients in his thirty to thirty-four years age group as "elderly primigravid women." The Twentieth Century Dictionary defines "elderly" as, "Somewhat old; advanced beyond middle age; bordering on old age." If I were an obstetric patient, even in the thirty-five to forty-plus age group, I think I would resent the adjective "elderly." If the term persists, we may find ourselves speaking of such an inconsistency as geriatric obstetrics!

A review of 1,624 consecutive obstetric patients, delivered in the Grand Forks Clinic between Jan. 1, 1940, and Dec. 31, 1947, showed 544 who were primigravid. In Dr. Randall's series of 1,558 primigravid women, there were 250 who were 35 years of age or older to our 23; he had 516, aged 30 to 34 years as compared with our 63; and 792 of his patients were under the age of thirty in contrast to our 458. We had no malignancies in our series.

Taking the length of the first stage of labor as a guide, I was unable to differentiate between the behavior of the uterus and cervix in any of our three groups. From the youngest to the oldest of the three groups this averaged 12 hours, 11 hours, and 12 hours and 21 minutes.

Dührssen's incisions and manual dilatation of the cervix which, in our hands, I would be forced to call manual laceration of the cervix, were not employed.

Cesarean section is important in this study. In the twenty-year period, covered by Dr. Randall's report, the incidence of cesarean section was 2.9 per cent in the women

under circumstances of a lessened remaining period of reproduction and associated disease or lessened functional capacity of the pelvic viscera. These conditions naturally are found with increasing frequency as aging occurs and, when associated with other factors such as toxemia or contraction of the pelvis even though these may not be severe, lead one to consider cesarean section. In our experience, in nearly 90 per cent of women 35 years of age or older the infant was delivered through the vagina; but four deaths among the 23 infants who died must be charged to operative delivery and the infants might have survived had cesarean section been performed. Perhaps minor degrees of bony pelvic contraction have been overemphasized and the unelastic soft tissues equally at fault have not been considered in selecting the method of delivery. If uterine behavior, errors of rotation, and the necessity of intervention higher in the birth canal are increased accompaniments of vaginal delivery, then one again must carefully weigh the decision as to method of delivery. We believe that an incidence of cesarean section of 12.8 per cent in the group 35 years of age or older is justified. We also believe that each case should be given comprehensive individual consideration and that age alone is not the sole criterion.

Our experience would indicate that, unless some complication necessitates the induction of labor, the pregnancy should not be disturbed until the spontaneous onset of labor. Assuming that the possibility of cephalopelvic disproportion is carefully considered, it would seem that the best interests of mother and infant are served if labor occurs when the cervix is ripe and the uterus is ready to function. Accidents and complications related to the placenta occurred no more frequently among the older women than when the patient was young. If one applies in full the advantages of modern prenatal care and scrutinizes the elderly primigravid woman carefully and further applies appropriate care at the time of delivery with all of our present-day protections, it would seem that these patients may undertake pregnancy and parturition with minimal risk.

We may not be satisfied with our fetal salvage. The frequent necessity of inducing labor with the resultant prematurity of the infant, the number of infants born weighing less than 2,500 Gm., and the associated toxemia in the mother, together with exposure to major obstetric operative procedures through the vagina, serve to increase the hazard to the infants born to elderly primigravid women. In our experience postmaturity or the oversized infant did not contribute significantly to infant deaths. An uncorrected fetal mortality rate of 9.2 per cent of children born to mothers aged 35 years or older must be compared to an uncorrected fetal mortality rate of 2.8 per cent when the mother is less than 30 years of age. On occasion these factors will lead to the performance of cesarean section in the interest of the infant. Age of the mother alone seems rarely a sufficient reason for cesarean section but should be one of the factors to be considered.

Conclusions

General bodily conditions related to aging will appear more frequently in elderly primigravidas. Reduced efficiency of the genital tract becomes apparent from the increased number of patients who have myomas of the uterus. More frequently one encounters the combination of uterine inertia and delay in dilatation of the cervix in these patients.

Because of these factors and an increase of frequency of contraction of the bony pelvis and resistance of the soft tissues in the pelvis, operative

METHOD OF DELIVERY AMONG PRIMIGRAVID WOMEN

	350 WOMEN UNDER 30 YEARS OF AGE		248 WOMEN FROM 30 TO 34 YEARS OF AGE		108 WOMEN OVER 35 YEARS OF AGE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Spontaneous	165	47.0	103	41.5	42	38.89
Low forceps	121	34.6	116	46.77	45	41.6
Midforceps	26	7.42	5	2.01	3	2.77
High forceps	1	0.28	1	0.4	0	0
Manual rotation	20	5.7	10	4.03	2	1.8
Version	6	1.7	5	2.0	4	3.73
Breech extraction	28	8.0	15	6.0	9	8.25
Cesarean section	3	0.85	3	1.2	5	4.6
(Twins	350		248		108	
	3	0.85%	3	1.2%	1	0.92%)

INDICATIONS FOR CESAREAN SECTION IN PRIMIGRAVID WOMEN ACCORDING TO AGE

	350 WOMEN UNDER 30 YEARS OF AGE		248 WOMEN FROM 30 TO 34 YEARS OF AGE		108 WOMEN OVER 35 YEARS OF AGE	
Cephalopelvic disproportion	1		0		0	
Breech	0		1		1	
Placenta previa	1		1		1	
Myomas	1		0		1	
Toxemias	0		1		1	
Abruptio placentae	0		0		1	
	3	(0.85%)	3	(1.2%)	5	(4.6%)

Efficient prenatal care should develop an appreciation of the physiological, the anatomical and the psychological responses of each patient. The evolution in training should so develop one's conception of the merit of procedure that the age factor would be eliminated.

DR. L. A. CALKINS, Kansas City, Kan.—I can agree heartily with all that Dr. Randall has said, but I should like to say it in a different way. The woman who is young enough to become pregnant is young enough to go through the complete physiology of having her baby. The older women are old enough to have developed complications in other parts of the body just as Dr. Randall has stated; heart disease, myoma, carcinoma; etc. I would like to disagree with Dr. Randall in his selection of primigravid women, as I believe that the multigravid woman has the same increased risks as the primigravid woman.

DR. J. BAY JACOBS, Washington, D. C.—Dr. Quigley stressed the fact that most obstetricians and patients, and of course the families, were greatly concerned because of the age of the patient and attendant disagreeable factors that perhaps have been exaggerated, especially in the opinion of the patient.

Davis recently published an article entitled, "Childbearing in the Twilight of the Reproductive Period," in which he included primiparas as well as multiparas, and found that pregnancy complications for both mother and baby were increased in these women. We can compare his figures very effectively with those of Dr. Randall's group. Even in multiparas, the complications increased somewhat in the older age groups.

There are some factors that we must be aware of. The elderly primipara presents a mental attitude different from that of the young woman and I personally feel that that may affect the character of her labor and, of course, Dr. Randall had referred to this factor as some of the previous speakers had. We also are concerned with the type of labor the elderly primipara has. Personally, I do not feel that the uterus would contract so effectively in an old primipara as in a young one. Certainly in most cases it does not, and

under 30; 4.26 per cent in the patients between 30 and 34 and 12.8 per cent among the patients over 35 years of age. In our eight-year report I found 3.9 per cent; 9.5 per cent and 13 per cent, respectively. His over-all incidence of cesarean section since 1934 was 3.5 per cent; ours, during the past eight years was 4.9 per cent.

We had an uncorrected fetal mortality of 1.5 per cent in our 458 patients under the age of 30; 3.5 per cent in the 63 patients between 30 and 34, and none in the 23 patients over the age of 35 years.

Pre-existing hypertension became clinically important in two of our twenty-three patients over the age of 35 years; and two other patients in this group had uterine myoma and/or adenomyosis which required surgical section. The myoma developed acute red degeneration for which a myomectomy was done late in the eighth month of pregnancy, with subsequent delivery per vaginam at term. No myomas of clinical significance were found in any of our patients in the 30 to 34 age group or in those under thirty.

In the 544 primiparous patients in our series, the incidence of late toxemias of pregnancy was 2.6 per cent and in the 1,624 patients, covered by the same eight-year period, the incidence was 5 per cent. There were no maternal deaths in the primigravid group and one among the 1,624 patients.

Dr. Randall has indicated that cesarean section has an increased importance in the delivery of primigravid patients 35 years of age or older and has suggested factors, other than bony pelvis contraction, which may make cesarean section more desirable in this group. Our statistics in percentage are almost identical for cesarean section in this group. Contraction of the bony pelvis, however, accounted for all of our cesarean sections in the 30 to 34 age group and in all but two in the group under 30 years.

In conclusion, may I suggest that we substitute the adjective, "discriminating" for "elderly" in describing that fine group of patients who, having reached the age of discretion, which Dr. Randall places at thirty years or over, decide to have their first babies.

DR. BUFORD G. HAMILTON, Richmond, Mo.—I have selected 706 cases for discussion, cared for personally through the years. Like Dr. Randall, I have divided these cases into three groups for study. Two hundred forty-eight were 30 to 35 years of age, 108 were 35 to 44 inclusively, and 350 were under the age of 30.

EVENTS IN THE LABOR OF PRIMIGRAVID WOMEN AS TO AGE

	350 WOMEN UNDER 30 YEARS OF AGE	248 WOMEN FROM 30 TO 34 YEARS OF AGE	108 WOMEN OVER 35 YEARS OF AGE
Pulse (beforre and after labor)	82.27-89.82	83.35-90.27	84-97
Duration of labor	16.02 hours	14.36 hours	15.34 hours
Blood loss	162.2 c.c.	163.59 c.c.	201.3 c.c.
Dilatation completed	6	8	3
Induction	3	3	4
Third degree tear	1	1	1
Weight of baby	7.37 pounds	7.42 pounds	7.5 pounds
Deaths of mothers	1 (anesthetic)	1 (toxemia)	0
Toxemias	18 (5.14%)	24 (9.7%)	10 (9.3%)

MORTALITY OF BABIES

	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Before labor	7	2.0	9	3.63	2	1.6
During labor	8	2.3	3	1.2	1	0.9
After labor	5	1.43	4	1.61	2	1.6
Premature	7	2.0	4	1.61	4	3.7

Item

Fellowships for Cytological Diagnosis Course

The American Cancer Society is offering two fellowships for a four-month course in the study of exfoliative cytology at the laboratories under the supervision of Dr. Herbert F. Traut, Dr. James F. Rinehart, and Dr. Seymour M. Farber, in the University of California Medical School. Half the time is to be spent at the laboratory in the University of California Hospital and the other half at the San Francisco County Hospital cytology laboratory.

The fellowships include a payment of tuition fee and overhead to the University, and the trainee will receive \$140.00 per month to partially cover his living expenses for the period.

The requirements for the fellowships are that the applicants:

1. Be graduates of Class A Medical Schools of the United States, its territories, or of Canada.
2. Be citizens of the United States.
3. Be not over fifty years of age.
4. Have completed two years of postgraduate training in pathology.

The instruction will be given by three physicians who are experienced in the method and are spending full time in the work, and by six experienced technicians. There will be intermittent periods of personal instruction but no classes. The rest of the time will be spent in the study of the available classified material and the current specimens.

Please address inquiries to:

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I think the incidence of contracted pelvis is probably a little greater in elderly primiparas than in the young ones. Perhaps this, along with the absence of other typically feminine characteristics, is the reason why the woman is an elderly primipara rather than a young one. In other words, she may lack the necessary factors that tend to encourage early marriage.

In handling these cases, in spite of the good reports that have been shown, the morbidity and mortality rate for the mother, as well as for the fetus, is the thing that causes the most concern to the patient and her family. Her mental attitude naturally will be affected by the outcome. Even though these women are initially physiologically elderly, after the baby is born their mental and physical attitude is changed entirely, they appear and react as younger women do, and are anxious to have more babies, if the outcome is good. On the other hand, we must remember that if the outcome is not so good the mental attitude will become worse and quite serious for the patient.

I want to stress one thing in dealing with elderly primiparas. I do not hesitate to say that I am concerned. When confronted with an elderly primipara, I feel almost as I would if a young primipara of 200 or 220 pounds, with the disagreeable factors that generally attend such cases, walked into my office for the first time. In other words, I have particular concern for the elderly primipara regardless of the fact that such excellent results are reported. The thing that we are confronted with is primarily the mental attitude of the individual, and the responsibility involved because of the effect of that mental attitude upon the processes of pregnancy and labor, along with possibly some pelvic contraction, or other disagreeable factors.

The question is, how will labor progress in these individuals? I feel these women are entitled to a test of labor, but not the prolonged test that you would allow the young women to have. In the absence of serious complications, I would determine just how the uterus behaves during labor. If the contractions were effective and regular and there was no tendency to develop inertia, I would allow an effective test of labor; if there were any question, would do an elective cesarean section.

DR. JAMES K. QUIGLEY, Rochester, N. Y.—I have been inclined to advance the age limit from 30 to 35 as to what constitutes the elderly primipara. I would be interested to know whether Dr. Randall's cases carried with them an added risk to the mother and her baby. I believe Dr. Calkins has pointed out that the elderly multipara often has the same risk as the primipara.

DR. RANDALL (Closing).—The comment made by Dr. Calkins is pertinent but we did not cover that aspect of it in the paper. We have always used a trial of labor in selected cases and that was done in women in this group.

(The papers of Dr. Schmitz, Dr. Schwarz, and Dr. Quigley, presented at this meeting, will be included in the next issue of the JOURNAL.)

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On Dec. 9, 1945, the patient was anesthetized with nitrous oxide and ether. One finger was inserted into the vagina through an intact hymen. The vagina and cervix were normal to palpation. The corpus seemed to be of normal size and forward position. There was a large mass filling the lower abdomen. A small vaginal speculum was inserted and the vaginal mucosa was found to be moderately stimulated. The cervix looked normal. The uterine cavity measured $2\frac{1}{2}$ inches in depth.

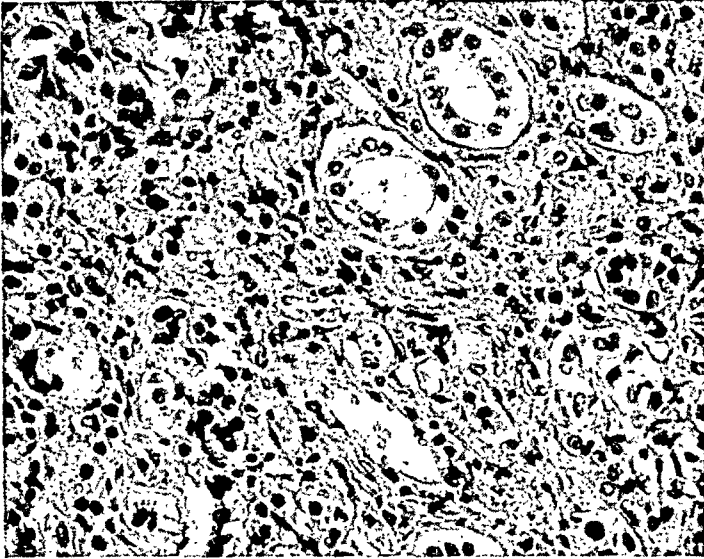


Fig. 4.—Photomicrograph shows tubules and sex cords.

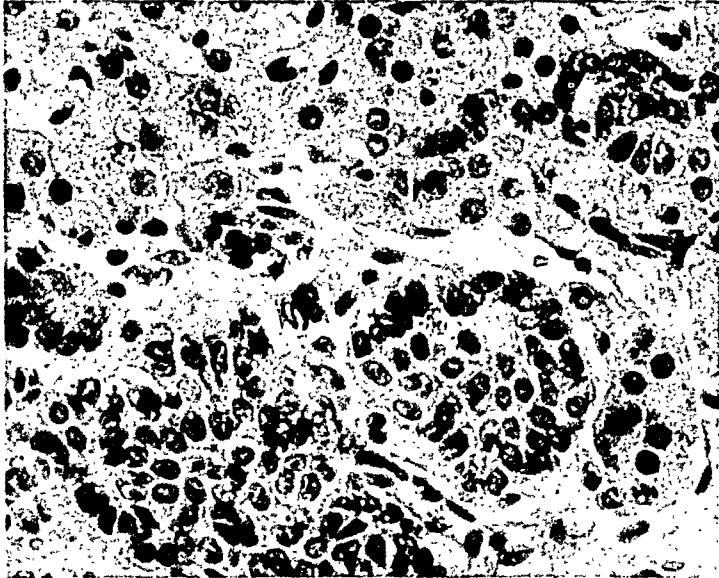


Fig. 5.—Sex cords and islands of interstitial cells are noted.

The patient was then prepared for a laparotomy. When the abdominal cavity was entered, 4,500 c.c. of blood-stained fluid was removed. A large cystic mass the size of a football was found arising from the right ovary. The mass was adherent to the peritoneum anteriorly and posteriorly. The tumor was infiltrated with blood and showed marked

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degeneration. While an attempt was being made to free the tumor with the hand, the very necrotic and friable pedicle tore away. Two or three blood vessels in the pedicle were clamped and ligated. The right tube was normal. The uterus, both tubes and left ovary were normal. The left ovary was rather smooth and did not show developing follicles on the surface nor were

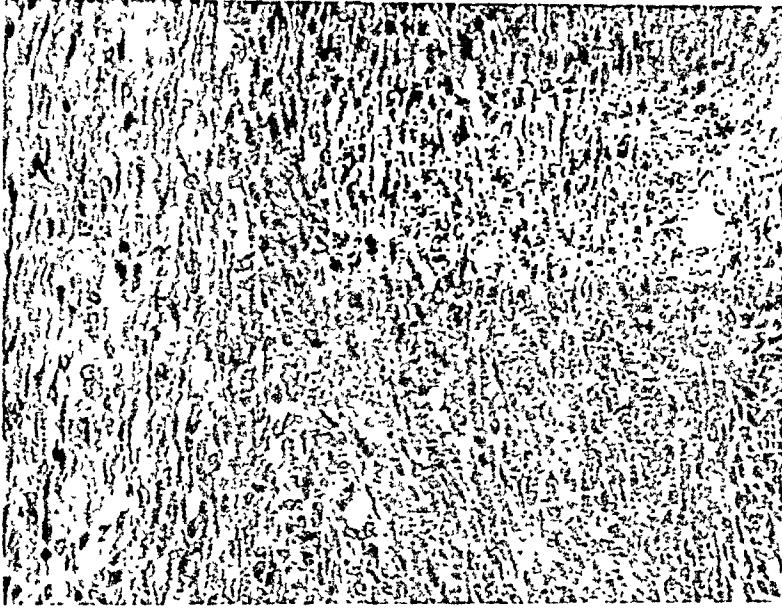


Fig. 6.—Section shows fibromatous character of the bulk of the tumor (femizing portion.)

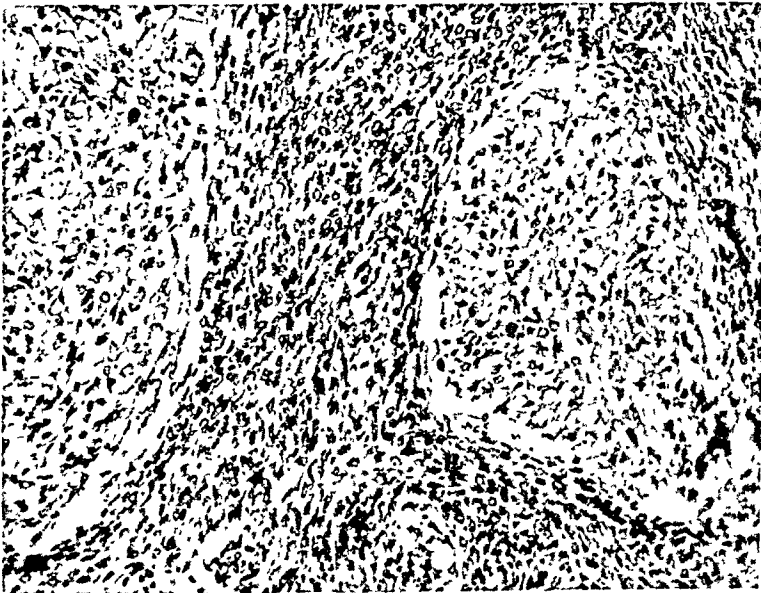


Fig. 7.—Lutein-like transformation of the theca cells.

many stigmata present. Implants on the right parietal peritoneum and in the cul-de-sac were removed. There were no palpable pathologic changes in the upper abdomen. The appendix was removed. During the early phase of removal of the tumor the patient showed signs of shock, drop in blood pressure, rapid pulse, pallor, etc. 500 c.c. blood plasma were given and followed by 500 c.c. of whole blood. The shock rather promptly subsided. The post-operative course was entirely uneventful. On the sixth postoperative day, the patient started to menstruate and flowed for two days. She was discharged from the hospital on the thirteenth postoperative day.

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Pathologic Study.—Gross: The tumor consisted of a semisolid mass measuring 18 by 17 by 6 cm. The external surface was roughened, showed hemorrhagic areas with evidence of surface adhesions. There was a broad pedicle which measured 8 by 12 cm. On cut section, the greater part of the tumor was solid but there were multiloculated cystic cavities. Some of the cysts contained a thin hemorrhagic fluid.

Microscopic: Some of the sections showed a definite arrhenoblastoma. In various areas, the characteristic sex cord-like arrangement of the cells was noted, in others, small tubules with a few tubules of rather large size (Fig. 4). There were many clumps of eosinophilic cells which morphologically were characteristic of the interstitial cells of Leydig (Fig. 5). These cells also showed a rich lipid content. Most sections of the tumor presented the morphologic picture of a diffuse granulosa or thecomatous tumor. This lesion was separate and distinct from the andromatous portion. There was an attempt in some areas at encapsulation (Fig. 6).

Second Hospital Admission.—The patient re-entered the hospital on Aug. 2, 1946, and gave a history of feeling very well since her first operation. Her menstrual cycle was every twenty-eight days and lasted four days. She noticed her breasts were enlarging and hair on her face was disappearing. Her voice was slightly higher pitched. Her mother stated she liked the company of girls now and had become very popular with boys. One month prior to this admission, the patient noted marked enlargement of the abdomen and rapid gain in weight. She experienced some pain in the lower abdomen. Physical examination revealed a rather pale girl in some pain. There was less hair on the face than on the previous admission. Her breasts were slightly larger, too. The heart and lungs were normal. The abdomen was distended by a mass extending almost to the xiphoid. A fluid wave was not perceptible, nor was there shifting dullness. Pelvic examination revealed that the clitoris had not decreased in size. One-finger examination of vagina showed the vagina and cervix normal to palpation. The vaginal mucous membrane appeared well stimulated. None of the pelvic structures could be palpated. Rectal examination was not revealing. A paracentesis was done with removal of 30 c.c. of bloody fluid. The sediment was examined for malignant cells but none was found. An x-ray plate of the chest showed normal cardiac silhouette, hilar shadows and lung markings. Both leaves of the diaphragm were high. Laboratory studies: Urinalysis showed no abnormalities. Blood count: red blood cells 3,690,000; hemoglobin 11.9 Gm.; white blood cells 9,300; with a normal differential count. Twenty-four-hour urine specimen showed no detectable steroid glucuronidate and 4 mg. of 17-ketosteroids. The preoperative diagnosis was either recurrence of the gynandroblastoma or a new tumor involving the left ovary.

A laparotomy was performed on Aug. 8, 1946, and 2,500 c.c. of bloody fluid was removed. On palpation, there was a very large mass extending from the pelvis to the xiphoid process. The mass was attached to the posterior surface of the uterus, broad ligaments, parietal peritoneum, omentum, and intestines. The tissue was friable, cystic, and contained bloody fluid. The mass was scooped out by the handful, enough to fill a large basin. The neoplasm did not infiltrate the tissue but was adherent to the surface and could be wiped and peeled off. The left ovary, both tubes, and the uterus were normal. Since it was decided to give the patient deep x-ray therapy, it seemed advisable to remove the left ovary for study. At the end of the operation, all of the visible neoplastic tissue was removed cleanly. Gelfoam was used in the cul-de-sac to control oozing. Immediately after the removal of the neoplastic growth was started, the patient went into profound shock, with imperceptible pulse and blood pressure for fifteen minutes. She was given 1,000 c.c. of citrated blood and soon her condition gradually improved. Her postoperative course was uneventful and she was discharged from the hospital on the twenty-third postoperative day. She received 500 c.c. of whole blood on the seventh postoperative day to correct her anemia. Deep x-ray therapy was started on the eleventh postoperative day and was continued with the patient ambulatory after discharge from the hospital. In a period of thirty-one consecutive days, a total of 8,200 r. was given over eight portals, four anteriorly and four posteriorly.

Pathologic Study.—Gross: The specimen consisted of 1.3 kg. of cystic, necrotic tissue. The largest piece of tissue measured 13 by 11 by 2 cm. Most of the cysts were ruptured

cells 6,910 with normal differential. Carbon dioxide capacity 68.5 volumes per cent, or 31.1 mg. per L. equivalent; chlorides 376 mg. per cent equivalent to 160 mg. per L. Twenty-four-hour urine specimen showed 9 mg. pregnanediol glucuronide and 2 mg. 17-ketosteroids. The preoperative diagnosis was recurrence of gynandroblastoma.

A laparotomy was done on Jan. 15, 1948. When the abdominal cavity was entered 3 L. of ascitic fluid were removed. There was a large amount of degenerated tumor attached to the parietal peritoneum, intestines, and especially a large amount attached to the under-surface of the liver. Again, the tissue did not infiltrate the organs but adhered to the surfaces. There was very little tumor found in the pelvis. All of the gross tissue was again scooped out and wiped off the organs. A small amount of the neoplasm could not be removed from the under surface of the liver. Considerable oozing from the liver was controlled by topical thrombin and packing. Again, the patient exhibited the same pattern of shock as in the three previous operations. She rallied from her shock on the administration of 1,500 c.c. of whole blood. Her postoperative course was complicated by some abdominal distention, nausea, and vomiting. On her eleventh postoperative day, deep x-ray therapy was again started. She was given 8,000 r. over a period of thirty-five consecutive days. This time therapy was given over both flanks and upper quadrants in addition to the usual portals over the lower abdomen and back. She was discharged from the hospital on the thirty-second postoperative day. Her long hospital residence was due to the fact that the x-ray department wanted her under close observation during the first part of her treatment. The patient has no complaints at the present time and has gained considerable weight. She stated specifically that she has never had a hot or cold flash.

Pathologic Study.—Gross: The specimen consisted of a large amount of hemorrhagic fragmented neoplastic tissue. The largest piece measured 8 by 6 by 4 cm.

Microscopic: Many sections failed to show any epithelial structures. Only thecomatous pattern was present. Again, areas of luteinization were noted.

Discussion

This case presents the usual clinical-pathologic picture of an intermediate type of arrhenoblastoma. In addition, it exhibits histologic and biologic evidence of an estrogen-producing tumor. The histogenesis of gynandroblastoma is of considerable interest. The masculinizing portion of the tumor may arise, as pointed out by Meyer in cases of arrhenoblastoma, from male-directed cells persisting in the ovary from early development; the feminizing portion may originate from remnants of granulosa cells left over in the process of follicle formation. In other words, it is theoretically possible for two tumors of different structures to develop in the same ovary. This seems to be the most likely origin in this case. The absence of intermingling of the andromatous and feminizing portions would point to this conclusion. Robert Meyer² suggests an origin from indifferent cells which may functionally and morphologically become hermaphroditic, so that both androgens and estrogens may be elaborated. Mechler and Black¹⁰ suggest a teratomatous origin.

It is of interest that this patient has never had symptoms of castration with the exception of amenorrhea. She has never had vasomotor symptoms, headaches, nervousness, nor depression which is usually associated with castration in a young woman. Her vaginal mucosa has appeared well stimulated at all times. This has only one implication and that is the tumor tissue is elaborating estrogens. An endometrial biopsy has not been obtained because at each opera-

but a few small ones contained a clear brown fluid. The left ovary measured 5 by 3½ by 2½ cm. On cut section, the ovary showed normal architecture with a recent corpus luteum and several developing follicles.

Microscopic: Sections of the tumor showed fibromatous, epithelioid type of cells growing diffusely. Morphologically, the cells were of the diffuse granulosa-thecomatous type. There was marked vascularity and extravasation of blood into the tissue. Multiple sections failed to show any andromatous structures. Sections of the left ovary revealed normal histology.

Third Hospital Admission.—The patient again entered the hospital on Sept. 3, 1947, and had had no complaints until two weeks previously, at which time she noted pain and swelling of her abdomen. Patient gained ten pounds in two weeks. Physical examination revealed a normal woman with the exception of a mass filling the abdomen to the level of the umbilicus. Pelvic examination showed no change in the size of the clitoris from the first examination. The vaginal mucosa looked fairly well stimulated. On rectal examination, a mass filling the lower abdomen was palpated. Chest plate was negative. Laboratory data: urinalysis was negative; blood count: red blood cells 4,150,000, hemoglobin 10.8 Gm., white blood cells 10,300. Differential count was normal. Blood nonprotein nitrogen was 17 mg. per cent. Blood sugar was 59 mg. per cent. Total protein was 6.2 Gm. per cent; albumin was 3.8 Gm. per cent and globulin 2.4 Gm. per cent. Blood Kahn test was negative. Twenty-four-hour urine specimen showed 7 mg. steroid glucuronidate and 9 mg. 17-ketosteroids. The preoperative diagnosis was recurrent gynandroblastoma of the peritoneum.

A laparotomy was done on Sept. 5, 1947. When the abdominal cavity was entered, approximately 8 L. of straw-colored fluid were removed. A large amount of friable tissue which contained fluid and blood was attached to the parietal peritoneum, serosa of the intestines, under surface of the liver, and a large mass 10 by 10 cm. was attached in the cul-de-sac and adherent to the posterior surface of the uterus and broad ligaments. The tissue was so friable that it was scooped out with the hand. Again, the neoplastic tissue was loosely attached to the liver, intestines, and parietal peritoneum. All gross tissue was removed, with the exception of a small area in the cul-de-sac. The uterus was normal in size. The right tube was removed. There was no evidence of metastases into the liver. The intestines were free and the parietal peritoneum clean at the end of operation. Again, the patient showed the same picture of shock as soon as the abdomen was entered as on the two previous operations. The patient recovered from her shock upon the administration of whole blood. The postoperative course was uneventful with the exception of moderate anemia which was corrected by whole blood transfusion. She was discharged on the fifteenth postoperative day.

She again received deep x-ray therapy as an ambulatory case for a consecutive period of nineteen days for a total of 6,400 r. over the abdomen and back.

Pathologic Study.—Gross: A large amount of friable hemorrhagic tumor tissue consisting in part of numerous small pieces to which were attached pieces of omentum and fragments of peritoneum; another part consisted of a rounded solid mass of tissue measuring 10 cm. in diameter. On section of this tissue there was hemorrhage giving it a mottled appearance. The tissue had a brain-like consistency. A few small cavitations were present which contained old blood or mucoid material.

Microscopic: Multiple sections of the tissue revealed only the thecomatous type of cells. No andromatous elements were found. In one area there was lutein-like transformation of the cells (Fig. 7).

Fourth Hospital Admission.—On Jan. 14, 1948, the patient stated that she had never felt better in her life until twenty days previously. At this time she noted rapid enlargement of the abdomen. She had some anorexia, nausea, and vomiting. Physical examination revealed a thin female with a markedly protruberant abdomen. All of the positive findings were confined to the lower abdomen. A large mass could be palpated. A fluid wave was present. The vaginal mucous membrane appeared fairly well stimulated. Rectal examination revealed a large mass filling the lower abdomen. Chest film was negative. Laboratory data: Urinalysis was negative. Blood count: Red blood cells 3,690,000; hemoglobin 11.1 Gm.; white blood

Summary

A young girl, 18 years old, has both a feminizing and virilizing tumor of the same ovary from a morphologic standpoint. The clinical features of this case suggest a combination of the hormonal effects of androgens and estrogens. The antagonism of these two hormones is complex. The primary tumor showed a predominance of androgens from a biologic consideration since there was defeminization and masculinization. After removal of the tumor, even though it has repeatedly recurred, there has been no biologic or histologic evidence of androgen elaboration, while, on the other hand, there has been clinical evidence of estrogen production. A study of 17-ketosteroid excretion in this case has not been of clinical value. Roentgen-ray therapy undoubtedly has an effect on slowing the tumor growth but apparently is not lethal to the cells, even in large concentration. This tumor histologically lacks most of the criteria for malignancy yet it is recurrent and locally invasive.

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630 SOUTH KINGSHIGHWAY

Discussion

DR. J. P. PRATT, Detroit, Mich.—The unusual clinical picture just presented by Dr. Hobbs invites speculation as to the genesis of mixed tumors of the ovary. Since he has confined his report mostly to the clinical features, the discussion may well follow the same direction. I have not had a similar experience but it has been my privilege to review the microscopic sections from a case reported by Dr. Christopher of Detroit. His report is now in press and he has generously offered to let me use some of his data. He, as well as Mechler and Black, has carefully reviewed the pertinent literature.

The name *Gynandroblastoma* was first suggested by Robert Meyer in 1930 when he presented to the Berlin Gynecological Society a series of arrhenoblastomas. One of his tumors contained elements similar to granulosa-cell tumors. The uterus was hypertrophied.

Plate, in 1938, reported a tumor showing both granulosa cell and arrhenoblastoma and he collected twelve cases from the literature which he believed could be classified histogenetically and morphologically as a combined tumor.

Mechler and Black, in 1943, reported a case of gynandroblastoma and reviewed the literature. Schiller, in a discussion of this paper, accepted only four cases of gynandroblastoma (Plate, Frankl, Schiller, Mechler and Black), and later accepted Christopher's case. Robert Meyer accepted the diagnosis of granulosa cell in Christopher's case but was not so sure of the arrhenoblastoma elements.

tion her condition has been too precarious to permit it. It would be impossible to get such a biopsy without anesthetizing the patient. A recent vaginal smear showed exfoliation found in women with mild estrogenic stimulation.

The age of patients in the reported cases has ranged from 17 to 76 years. Only one other patient was younger than this one. Most of the tumors have been relatively small. This one was very large.

No case of gynandroblastoma reported had had so many repeated endocrinologic and pathologic studies. The patient exhibited the classical picture of acquired virilism; hirsutism; enlargement of the clitoris and amenorrhea, yet there was no increase in the 17-ketosteroids or the steroid glucuronidate in the urine. All of the urine specimens obtained were secured, of course, when there was a large amount of active tumor tissue growing in the abdominal cavity. The failure to find increased amounts of steroids in the urine does not indicate that unusual amounts of androgens were not being elaborated by the tumor. For example, Geist and his co-workers¹² have shown that 500 mg. of testosterone per month is sufficient to induce virilism in normal women, yet this amount would increase the daily excretion of ketosteroids by only a few milligrams at the most.

The sequence of events in this patient is such that the tumor must have been elaborating steroids, presumably androgens, or possibly progesterone, and estrogens which induced the amenorrhea by inhibition of the anterior pituitary. Then, following the removal of the tumor, the pituitary recovered its normal activity and normal cycles were resumed. The fact that the patient started her menses six days after removal of the tumor is *prima facie* evidence that the bleeding was due to deprivation of estrogen or possibly progesterone. It was evident that endometrium was already stimulated by sex hormones elaborated by the tumor. In virilizing tumors, either adrenal or ovarian, the pituitary usually does not recover for one to two months. But despite recurrence of the tumor normal cycles persisted to the time of removal of the other ovary, indicating that the recurrent tumor had biologic characteristics different from the original tumor. Histopathologic study also shows that the recurrent tumor lacks the masculine elements found in the original new growth.

The tumor has grown in a peculiar manner. It has propagated on the surface of the organs. It is always amazing to see how clean the abdomen is after removal of the tumor. Numerous operations are anticipated unless the tumor takes on a different method of propagation.

There has been unusual opportunity to study the effect of deep x-ray therapy on the tumor. Although she has had a total of 22,600 r. over a period of a little less than two years, there has been slight evidence of regression such as pyknotic nuclei, vacuolization of cells, and edema. The greatest suggestion of benefit has been the relatively little tissue found in the pelvis on the last two operations as compared to the increased amount in the upper abdomen. Perhaps the explanation for this is the fact that most of the therapy has been concentrated in the pelvic region.

Dr. Hobbs stated that the ketosteroid factors obtained in connection with his case were normal. Unfortunately no readings were taken except immediately after surgery when 17-ketosteroids are notoriously low. Besides, the average normal varies for a given method of purification. For instance, in our laboratory, the average normal was found to vary from 5 to 18 mg. in 24 hours, while Hamblen and Talbot give 4 to 5 mg. and Pincus and Friedgood 9 mg. The same holds good for pregnandiol determinations. If Dr. Hobbs had taken these factors into consideration, more might have been learned about the functional significance of his tumor in relation to the symptoms presented. Failure to obtain endometrium for a similar purpose was a regrettable oversight since the endometrium at least might have given a hint as to the functional preponderance of either component of the tumor described. While the case presented by Dr. Hobbs is most interesting, I believe that more basic information of real value could have been added to our still fragmentary knowledge of functional tumors by a more exhaustive endocrine study.

DR. CHARLES A. BEHNEY, Philadelphia, Pa.—The subject of this presentation, a most unusual combination of two neoplasms, one extremely rare, with bisexual characteristics, afforded an opportunity to observe the physiology and chemistry of a tumor. We have never encountered growths of this type nor are we aware of any having been found in the Philadelphia area.

In retrospect, it is regrettable that certain studies were omitted for one reason or another. Information provided by complete hormonal assays, vaginal spreads, endometrial biopsy, the basal metabolic rate, glucose tolerance test, and x-ray examination of the skull might have disclosed some interesting and helpful data. Investigation of the adrenals by intravenous pyelogram, costovertebral insufflation, the chloride excretion test, and palpation also appear to have been indicated.

If the condition of the patient after laparotomy precluded curettage, endometrial biopsies might have been secured preliminary to the major procedure or during the intervals between operations. In view of the frequent association of fundal cancer with granulosa-cell tumors a curettage should still be done. The additional hazard, if any, involved by hysterectomy, rather than appendectomy on one occasion or oophorectomy on another, would have been justified.

This tumor appears to have behaved very much as in a tissue culture, thriving here and there until the nutritional capacity of the environment of the transplant was exhausted, and then becoming necrotic. The lack of evidence of invasiveness or metastases makes the propriety of malignant classification as questionable as in the case of a pseudomucinous cyst or an endometrioma, both of which can be transplanted and do recur.

DR. HOBBS (Closing).—I quite agree with Dr. Emge that further hormonal studies should be done and that is my intention. To be sure, the value of 17-ketosteroids will vary in different laboratories. Compared to the normal established in our laboratory, this patient had a low normal value. These hormonal studies were of no differential significance in this patient.

Dr. Behney has made some excellent suggestions for further study of this patient. Several of these procedures have already been done. Unfortunately, an endometrial biopsy cannot be done without anesthetizing the patient. At the next operation I intend to do an endometrial biopsy first. More frequent study of vaginal smears may be of value in evaluating the estrogenic activity.

Christopher's patient, aged 28 years, was first seen in March, 1936. She complained of lower abdominal pain for 30 days and menorrhagia for 11 months. Menstruation began at age 14 and was regular every twenty-eight days until she bore her first child in 1927. Delivery of this child was followed by amenorrhea for nine months. Following the birth of the second child in 1929, she had menorrhagia and metrorrhagia, her voice became deeper, and libido decreased. She had a deep voice, scant hirsutism, and mild hypertrophy of the clitoris. The breasts were small and flat. At operation, a tumor of the right ovary, the size of a lemon, was removed. The left ovary was small and fibrous. The uterus was uniformly hypertrophied. (No hormone studies were done). Following operation, vaginal bleeding ceased and a normal menstrual period occurred three months after operation. Menstruation has been normal since (12 years). Her voice remained deep, the clitoris remained enlarged, the breasts enlarged and the libido increased. Curettings taken at the time the tumor was removed showed a post-menstrual endometrium corresponding to the eighth day of the cycle.

All but one of the tumors reported were unilateral and most of them were benign. Although the six cases reported are not alike, it would seem that there are enough points of similarity to justify a tentative preoperative diagnosis of gynandroblastoma when certain conditions are fulfilled. An ovarian tumor associated with evidence of masculinization and hyperestrinism is suggestive. Endocrine assays may be indicative in some future case, but in the previous reports the procedure has not helped the diagnosis. No constant pattern in the tumors has been reported but all showed some combination of granulosa cell and arrhenoblastoma. Since the macroscopic appearance of arrhenoblastoma and granulosa-cell tumors is similar, the clinical history should suggest a more diligent search microscopically for the combined elements of tumors.

Why has virilism been diagnosed by clinical manifestations but not by hormonal assays? Androgens are capable of inhibiting menstruation in normal women by inhibiting pituitary secretion of gonadotropins, thereby removing the stimulus to ovarian activity. Granulosa-cell tumors apparently produce estrogens, independent of pituitary influence. The influence of androgens in all six cases produced virilism and in three cases, amenorrhea. In one report, the menstrual history was not recorded. Clinical evidence will depend upon the amount of androgens and estrogens, antagonism between the hormones and the ability of the receptor to respond to the hormones. Besides amenorrhea, the most conspicuous symptoms of virilism were hirsutism, low-pitched voice, and hypertrophied clitoris.

It is remarkable how long increasing signs of masculinization are tolerated by the patient before seeking medical attention. (Dr. Hobbs' patient waited three years, Dr. Christopher's seven years). During that time, the anatomic structures were changing and when masculinization once becomes established, it is irreversible. The transition is so gradual that no sign or event is conspicuous to the patient or her family.

We are fortunate to have had our attention directed to this unusual ovarian tumor. This presentation should be a stimulus to us to look more carefully for clinical and pathologic evidence of gynandroblastoma.

DR. LUDWIG A. EMGE, San Francisco, Calif.—No typical gynandroblastoma has come to our attention though we have seen tumors of the ovary harboring components of both male and female gonadal derivatives. We have classed these as mesenchymomas for want of a better term simply to indicate their period of formation as lying somewhere between dysgerminoma and well-differentiated functional tumors of unilateral sex development. Such a tumor was recently reported by Dr. Albert Long, in *California Medicine*. The respective patient consulted us for rapidly increasing hirsutism accompanied by hemothorax similar to Meigs' syndrome. The tumor revealed a preponderance of granulosa-cell elements and dispersed androgenic components. The endometrium presented a typical hyperplasia. All symptoms disappeared with the elimination of the tumor with the exception of the hirsutism. 17-ketosteroids leveled off from 21.3 mg. in twenty-four hours before operation to 16 mg. twenty months later. It is difficult to explain the persistence of hirsutism unless it occurred independently from the androgenic factor in the tumor. The fact that the 17-ketosteroids remained close to the upper limit of the average normal hints at an adrenal factor.

TABLE III. ECLAMPSIA,* PARKLAND HOSPITAL

AGE	PARITY	CONVULSIONS		MORPHINE (GRAINS)	INFANT FATE
		ONSET	NUMBER		
1946					
32	5	Antepartum	1	0.75	Alive
15	0	Antepartum	3	1.25	Alive
18	0	Antepartum	9	0.80	Alive
40	0	Postpartum	2	0.50	Alive
22	0	Intrapartum	1	2.25	Alive
35	4	Postpartum	4	2.00	Triplets—Alive
19	3	Intrapartum	3	2.00	Alive
20	0	Intrapartum	1	0.75	Alive
14	0	Intrapartum	2	2.75	Alive
19	0	Intrapartum	1	3.75	Alive†
1947					
18	0	Antepartum	9	3.25	Dead
17	0	Antepartum	1	2.13	Alive
19	0	Antepartum	2	5.00	Alive‡
28	1	Postpartum	1	1.16	Alive
22	0	Postpartum	1	0.50	Alive
13	0	Postpartum	2	2.25	Alive
22	0	Antepartum	1	1.63	Dead
16	0	Antepartum	10	4.50	Dead
19	0	Intrapartum	1	0.75	Dead
15	0	Antepartum	3	2.50	Dead
26	1	Antepartum	5	2.00	Dead
1948, First Trimester					
15	0	Intrapartum	1	0.50	Twins—Alive
16	0	Antepartum	3	0.50	Alive

*There was no maternal death in this consecutive series of 23 women with convulsive toxemia.

†This infant survived the intrapartum administration of 3.75 grains of morphine sulfate

‡This infant survived the antepartum administration of 5.00 grains of morphine sulfate.

Note.—Since preparation of these data, another patient recovered. Her child also survived. The Fetal Mortality Rate is, therefore, 22.2 per cent, (21 living children; 6 dead).

There was no maternal death in this consecutive series of 23 women.* Twenty-six children were born to these 23 mothers, including a set each of triplets and twins. There were six fetal deaths, 23.0 per cent, or a 77.0 per cent survival rate, despite the employment of heavy doses of morphine sulfate. Even if the fortuitous circumstance of survival of all the infants of the multiple births is discounted, the death rate of six children from 23 births would be only 26.1 per cent. For the sake of completeness, details concerning the six fetal deaths are given in Table IV. Parkland Hospital serves the indigent population of Dallas. Half of our clientele is Negro, one quarter is Mexican, and there is no opportunity for selection of patients. Nearly one-fourth of the patients appear for the first time in labor, many of the remainder come infrequently to prenatal clinic, and we count ourselves fortunate to see them more than once before term. Obviously, we cannot continue to manage pregnancy toxemia under such conditions without maternal fatality.

The current treatment for convulsive toxemia at Parkland Hospital is summarized below. Upon admission, or after the initial convulsion, $\frac{1}{4}$ grain of morphine sulfate is injected intravenously and $\frac{1}{4}$ grain subcutaneously. Addi-

*Since then, another patient recovered from convulsive toxemia. Survival of her child reduces the infant mortality rate to 22.2 per cent.

THE PHYSIOPATHOLOGY OF ECLAMPSIA*

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Southwestern Medical College)

DURING nine months of 1945, five women suffering from pregnancy toxemia died on our service at Parkland Hospital. Tables I and II. This represented the mortality experience with toxemia during two years. Since then, a mildly toxemic patient died with proved pleurisy of hemolytic staphylococcus origin. After careful review of the case histories, it was at once evident that pulmonary edema accounted for four of the five deaths and was a feature in the fifth. Treatment philosophy, at the time, was concerned with efforts to overcome oliguria by copious intravenous injections of normal and hypertonic fluids. Cessation of this practice brought gratifying results. There has been no death from, or associated with, pregnancy toxemia at Parkland Hospital since October 28, 1946. Moreover, pulmonary edema has not been observed since. No other change was instituted in the treatment of either convulsive or nonconvulsive toxemia, and it remains ultraconservative. The experience with convulsive toxemia during 1946, 1947, and the first trimester of 1948 is given in Table III.

TABLE I. TOXEMIA* STATISTICS, PARKLAND HOSPITAL, 1944, 1945, 1946, 1947, 1948
(FIRST TRIMESTER)

Patients discharged	8,090
Patients delivered	6,555
Toxemic patients, total	520
Convulsive toxemia	34
Nonconvulsive toxemia	486

*Toxemia was diagnosed when a pregnant woman exhibited two of the following signs: hypertension, albuminuria, edema.

TABLE II. DEATHS FROM TOXEMIA OF PREGNANCY, PARKLAND HOSPITAL

	NUMBER OF DEATHS*						
	1944	1945	1946	1947	1948 FIRST TRI- MESTER	TOTAL	
						NUMBER	PER CENT
Convulsive toxemia (34 patients)	0	3	0	0	0	3	8.3
Nonconvulsive toxemia (486 patients)	0	2	1	0	0	3	0.6
Total (520 patients)	0	5	1	0	0	6	1.2

*Note that most of the fatalities (five-sixths) occurred in 1945.

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

It is general belief that changes in the retinal arterioles are samples of arterial changes throughout the body. Hallum⁸ re-emphasizes this belief in an excellent article based upon personal examination of the eyegrounds of 2,500 pregnant women with hypertension. Unfortunately, space does not permit direct quotation of his descriptions of the spasm of pre-eclampsia and the more permanent sclerosis of chronic hypertensive disease. He also points out that spasm may be superimposed upon arterioles already constricted by the sclerosis of chronic vascular disease. According to him, von Graefe in 1855, four years after the invention of the ophthalmoscope, first described the retinopathy of pregnancy.

The idea that the fundamental pathologic lesion of the pre-eclampsia—eclampsia syndrome occurs in the terminal arterioles is not new. It was first outlined in detail in this country in 1936 by Irving,¹⁰ who explained the production of the pathologic lesions and the clinical signs on the basis of arteriolar spasm. He says that Volhard in 1918 was the first to advance the concept. The year following appearance of Irving's article, Addis¹ in England and Eastman⁵ here, made similar observations. Dieckmann⁴ mentioned the hypothesis in 1941, but it was not until 1943 that the fundamental nature of arteriolar spasm began to receive attention. Since then, many authors^{1, 7-9, 11-14} have affirmed the belief that arteriolar spasm is basic to the development of the pre-eclampsia—eclampsia syndrome. If this can be accepted as a working hypothesis, many of the known facts concerning the disease become explicable on a physiopathologic basis.

The pathogenesis of the kidney and liver lesions, and the development of hypertension, albuminuria, and edema are so well explained by Irving, and more recently by Page,¹³ their inclusion here would be repetitious. The remainder of this paper, therefore, will be concerned with attempted explanation of some of the less frequently discussed effects of angiospasm.

Angiospasm

Angiospasm, depending upon location, intensity, and duration, produces varying degrees of tissue ischemia. Mild ischemia of short duration may be tolerated by some tissues without appreciable immediate or permanent damage. On the other hand, malacia, or tissue softening, and necrosis may result from prolonged and severe tissue ischemia. According to Best and Taylor,² cells of the cerebral cortex cannot survive complete oxygen lack for more than five minutes, and may sustain definite injury after one-half minute. Cells of the brain stem are less sensitive and may survive total ischemia up to 25 minutes. Obviously, parenchymal cells of kidney and liver are more sensitive than the less highly specialized cells of muscle and integument. The delicateness of highly specialized cerebral cells is attested clinically by the fact that cerebral hemorrhage is found in about 15 to 20 per cent⁴ of autopsies on patients dying with eclampsia. Apparently the sequence of events includes: spasm of an end-artery, tissue ischemia, tissue malacia or necrosis distal to the spasm, release of spasm and hemorrhage. Or there may be only sufficient ischemia to produce arteriolar endothelial damage with or without subsequent thrombosis. With these general remarks, consideration will be given to specific locations and entities.

tional drug is administered (with 30 minutes between treatments for time to observe effect) in order to reduce the respiratory rate below 14, but not below 10 per minute. Occasionally, an enema of 200 c.c. of tap water containing 20 or 30 grains of chloral hydrate is substituted to avoid excessive morphinization. External stimulus, such as bright light, noise, needle pricks, and catheterization, is avoided. A medical student remains in constant attendance. *Fluid intake is limited to replacement of the daily insensible loss* (assessed at 1,500 c.c.) plus an amount equivalent to the urinary excretion of the previous twenty-four hours. This is not dehydration treatment; rather it is a policy of maintenance of fluid balance. Five per cent dextrose in distilled water is the standard infusion medium, and no hypertonic solution or plasma is employed. The obstetric status is ignored during the convulsive phase and treatment conducted without regard for the pregnancy. After convulsions are controlled and the patient becomes conscious, sedation is achieved with phenobarbital. The patient remains absolutely in bed, and generally accepted dietary principles, including high protein and low salt content, are followed. Labor is induced by rupture of the bag of waters two, or preferably three, days after the last convulsion. No ancillary treatment is employed, and operative delivery is performed only upon obstetric indication.

TABLE IV. FETAL DEATHS^a

NAME	BIRTH WEIGHT (GM.)	CAUSE OF DEATH
M. F. B.	2,806	Macerated stillbirth
M. S.	1,587	Macerated stillbirth
S. T.	1,602	Born alive. Died shortly
J. J.	4,270	Born alive. Died 19 minutes later. Cause unknown
C. W.	1,588	Born alive. Died next day
E. C.	1,587	Born alive. Died shortly

^aNote that only one fetal death, the infant of Mrs. J. J., can be attributed to factors relating to labor.

Discussion

It seems that avoidance of excess injection of fluid improved our toxemia recovery rate. If this is true, and not the result of chance, why are toxemic patients sensitive to fluid overload? Arteriolar spasm provides a satisfying answer to the question. There is irritability, but no resiliency of the muscular walls of the arterioles, with marked decrease of ability to accommodate fluid injected into the vascular tree. Moreover, the rate of water excretion by the kidney is seriously curtailed as a result of glomerular ischemia. These combine to make the toxemic woman resistant to sudden increase of blood volume. Right heart failure with pulmonary edema can, therefore, follow injection of a much smaller volume of fluid than is the case with a normal individual. Whether or not this is the correct explanation, these facts cannot be denied: 1. Pulmonary edema accounted for the deaths of four toxemic women and was a feature in the death of a fifth. 2. Since we adopted a policy of simple maintenance of fluid balance, no toxemic patient has died and none has developed recognizable pulmonary edema. 3. Angiospasm, or sclerotic arteriolar constriction, may be observed in the retinal arteries of most pregnant women with hypertension.

supplying the sinuses of the placental site. This is a simple reason for accidental, retroplacental hemorrhage and, if true, explains the frequent but not invariable association with acute and chronic toxemic states. On the other hand, it would be foolish to suggest that formation of *all* retroplacental hematomas is due to this cause. Perhaps these mechanisms might also afford explanation for some placental infarcts.



Fig. 2.—Cerebellum and brain stem of patient of Fig. 1. The hemorrhage is in the right mid-brain at the level of the red nucleus. Reprinted from Eller.⁶

The not infrequent occurrence of children smaller than compatible with the known duration of pregnancy, or of unexplained stillbirth, is a well-known clinical phenomenon. In the past it has been ascribed vaguely to the "toxicity" of pregnancy toxemia. With acute pre-eclampsia—eclampsia syndromes, long-continued spastic reduction of maternal arteriolar caliber could diminish materially the available supply of nutrient materials. More severe spasm might cause fetal death from anoxia. With chronic, pre-existing hypertensive vascular disease, the known tendency to fetal death toward the end of pregnancy is readily understandable in terms of chronic, sclerotic arteriolar constriction. Superimposition of acute, upon chronic, toxemia would seem to favor appearance of these phenomena centering around the placenta. On the other hand, many toxic women and their infants escape placental difficulties. Perhaps this is so because the chief localization of arteriolar damage or spasm happens to be other than the placental site. Perhaps it is of mild degree, or the enormous compensatory powers of the body tend to nullify damage.

Treatment.—Through the years, treatments for pregnancy toxemia come and go, but always there remain three clinically proved and accepted measures: bed rest, sedation, and interruption of pregnancy. In the light of angiospasm, it is easy to understand the first two. The horizontal position immediately decreases the cardiac load, minimizes antagonism between angiospasm and resulting hypertension, and increases the urinary output. Sedation provides a gentle means of relaxing angiospasm.

Brain.—Eller⁶ described the effect of encephalomalacia in two of the women of the Parkland series. Fig. 1 shows the cerebral tissue damage encountered in a 20-year-old primigravida dying with a terminal fever of 107.6° Fahrenheit on the fourth puerperal day. Fig. 2 shows the extent of the hemorrhage occurring with release of spasm and return of full arterial tension to the softened area. Since the hemorrhage was at the level of the red nucleus in the right midbrain, it explains both the high terminal fever and the fatality.

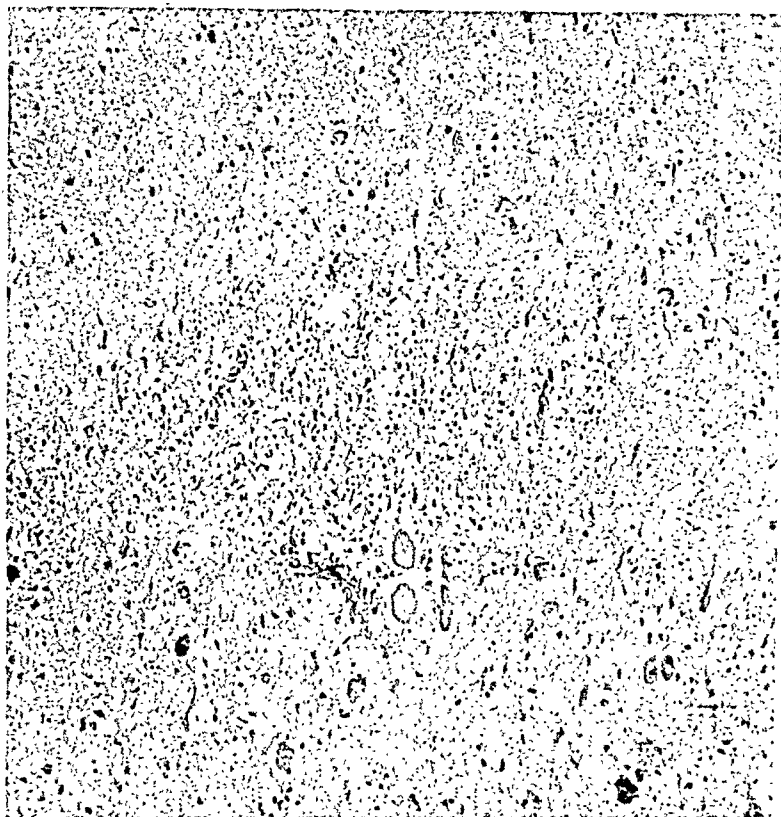


Fig. 1.—Brain stem tissue of 20-year-old primigravida, B. J., magnification $\times 110$.

Note the well-localized vacuolated area of the neuroglial stroma in the center of the section. The nerve cells have largely disappeared. This is also an area of early necrosis and demyelination. The injury would seem to be several days old, because early attempts at repair by neuroglial proliferation can be seen. Note the large dark oval bodies in the center bottom of the section. Probably these are degenerating nerve cells.

No one knows the precise mechanism of production of the hypertension or the convulsions of eclampsia. A possible explanation of hypertension might include: generalized cerebral arteriolar spasm, tissue ischemia, cerebral edema, increased intracranial pressure, compression of the medullary center and compensatory hypertension after the mechanism described by Cushing.³ With regard to the convulsions, perhaps *more than one mechanism* is involved. It is generally agreed that oxygen lack or increased intracranial pressure can produce convulsions. They may also be produced by water intoxication, a fact thoroughly established by animal experimentation and attempts at human therapeutics. It is probable that some of the convulsions occurring in toxemic patients, days after delivery, are due to water intoxication and not at all to the disease.

The Placental Site.—Angiospastic mechanisms similar to those causing intracranial hemorrhage may be invoked to explain hemorrhage in maternal arteries

methionine intravenously. There was a withdrawal of fluid from the tissue spaces but there was still a temporary anuria present. This overloaded the circulation with a subsequent right-sided heart failure and creation of a marked pulmonary edema. Fortunately, adequate kidney excretion took place within a few hours and both patients recovered.

With reference to vascular spasm, I shall show one case tomorrow where there was widespread brain damage, presumably caused by persistent vascular spasm and anoxia. This patient was discharged from hospital when she was in a definitely demented condition. The electroencephalogram denoted several large areas of apparent cerebral infarction.

While I still think that water is the best diuretic agent, our experience in Montreal also shows that a rational amount of fluid intake should be administered after taking into consideration the amount of edema present, the condition of the heart, and excretion capabilities of the kidneys.

DR. HOWARD C. TAYLOR, JR., New York City.—Dr. Mengert's view that the toxemias of pregnancy are dependent for many of their manifestations upon angiospasm is no doubt true. There is, however, one aspect of the disorder that has been investigated repeatedly which offers some contradiction. The study of the blood fluid through the kidney during the acute phase of the toxemias of pregnancy has shown no ischemia but an actual increase in the blood flow. I think that toxemia of pregnancy is the only decrease with hypertension in which renal ischemia is not demonstrated by this method:

It is, furthermore, striking that many of these patients who have a hyperemia of the kidney during their acute phase develop an ischemia of the kidney after delivery, providing that the hypertension remained. In other words, the cases subdivide themselves after delivery into those in which there is complete recovery, where the renal blood flow remains normal; and those in which there is a residual hypertension, where the renal blood flow drops to levels characteristic of essential hypertension.

These observations by four independent workers are, I think, of some definite significance, since they indicate that the hypertension of the toxemia of pregnancy is in some way different from that of the nonpregnant individual. There is also a slight indication that at least in one area of the body vasodilatation may be present as well as angiospasm:

DR. RUDOLPH BARTHOLOMEW, Atlanta, Ga.—I would like to call attention to the fact that angiospasm undoubtedly is a very important underlying basis for toxemia of pregnancy but cannot explain all of the phenomena. I would call attention particularly to the fact that in fulminating cases convulsions may occur without much angiospasm. One who notes the condition of the retinal arteries can often find cases of fulminating eclampsia showing a few beginning spasms, and yet these patients are having repeated convulsions.

If the condition of the arteries in the eye is a criterion of that pertaining to the arteries throughout the body, we must admit then that there is some other factor which has not as yet been stressed. I do want to emphasize that the angiospasm is not the entire story.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—Dr. Mengert's paper supports the thesis that angiospasm, capillary hemorrhage and thrombosis, and local tissue necrosis are important histologic lesions in the underlying pathology of eclampsia. The fact that Dr. Taylor's studies of renal function do not point to a consistent deficiency of circulation in the renal area does not necessarily disprove this now commonly accepted concept. It is well known that vascular changes in one organ may differ very considerably from those in another.

Studies that we have been conducting in our department of cerebral circulation in toxemia of pregnancy help to support the thesis which Dr. Mengert's paper favors. Employing the method of Kety and Schmidt, we have found a general reduction of cerebral circulation, oxygen consumption, and metabolic exchange in the presence of severe pre-eclampsia, eclampsia, and some of the other hypertensive conditions. These findings are to be reported in a short time and will constitute, I believe, the first confirmation of our many theories as to what goes on in the brain in eclampsia.

Soon after termination of pregnancy, angiospasm ceases. Thus, interruption shortens the duration of ischemia and thereby minimizes the danger of permanent tissue damage.

A final word must be said concerning two treatments: one old, *Veratrum viride*, and the other new, high spinal anesthesia. Both provide vasodilation, the former generally, and the latter locally below the level of the injected drug. It would seem logical to employ one or both. On the other hand, there is evidence that the hypertension of pregnancy is both attempted compensation and protective response. Partially for this reason, but chiefly because of previous success, we have not yet seen fit to adopt either of these treatments.

Summary

Five toxemic women died on our service during a nine months' period as a result of, or in association with, pulmonary edema. This motivated a change in treatment schedules, and a simple policy of fluid maintenance was adopted. The daily fluid intake, therefore, is now limited to 2,500 c.c. of fluid. Five per cent dextrose in distilled water is the infusion medium when the patient is unable to drink, and no hypertonic solution or plasma is employed. No other treatment feature was changed, and the basic philosophy of ultraconservatism was continued. Since then, no toxemic patient has died and none has developed recognizable pulmonary edema. Twenty-four consecutive pregnant women with convulsive toxemia have recovered and there is a 77.8 per cent fetal survival rate.

Angiospasm was advanced by Volhard in 1918 and by Irving in this country in 1936 as the basic pathologic lesion of eclampsia. Its existence can be seen in the retinal arterioles of most pregnant women with hypertension. It is believed that many of the pathologic lesions and known clinical phenomena of pregnancy toxemia can be explained on this basis.

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Discussion

DR. NEWELL W. PHILPOTT, Montreal, Canada.—I would like to corroborate the statement of Dr. Mengert when he says that large intake of fluid is ill advised in the patient with edema, especially when the kidneys are not excreting to normal capacity. We have had two cases where reactions were of a serious nature. These were severe pre-eclamptic patients with marked edema. After delivery they were given glucose and water with 10 Gm. of

THE SECOND STAGE OF LABOR*

III. Number of Pains

L. A. CALKINS, M.D., PH.D., KANSAS CITY, KANSAS

(From the University of Kansas Medical Center)

SOME years ago, we suggested to our house staff that whenever there was doubt as to completeness of dilatation of the cervix, a vaginal examination, under aseptic technique, should be done. This resulted in a lessened frequency of prolonged second stage in our clinic. There was still remaining, however, a higher incidence in the clinic patients than was being observed in our private patients. We, therefore, made it a rule that a vaginal examination should be done when the head did not reach the pelvic floor within thirty minutes after the cervix had been thought to be completely dilated. (We had always operated in the belief that the cervix should not be considered to be completely dilated until it had completely retracted over the head.) It was very apparent, after the initiation of the above rule, that the final stages of cervical retraction were often very slow in the presence of poor labor pains in primiparas. It was also very apparent that a partially retracted cervix could not be palpated, in the anterior half of its circumference, by rectal touch.

Another survey of our records, a little more than a year ago, showed an almost complete absence of prolonged second stage. There was still, however, a marked variation in the duration of this part of the labor. While most of the patients, both primiparas and multiparas, had a quite short second stage, there was still a considerable number of primiparas in whom the second stage exceeded one hour. A survey of the latter group, separated from the larger fraction of the patients, showed a remarkably high incidence of long interval between pains (four to as much as eight minutes). We immediately wondered whether the prolonged second stage could not be partially explained on the basis of this long interval. We had previously found¹ that intensity of uterine contractions was a highly important item in the duration of the second stage. It is quite apparent to everyone that pains of good intensity are usually close together. It is also evident that pains at infrequent intervals are usually of poor intensity. Since there is no simple method of measuring intensity of uterine contractions accurately,[†] it was difficult to tell whether intensity or frequency was the more important consideration. The very fact that the results were measured in minutes introduced a third variable—time. It occurred to us, therefore, that we should, perhaps, try to eliminate both the frequency factor and the time factor from our consideration. This could very readily be done, if we noted the intensity of the pains, and then counted the number of pains, and used as our measure of the duration of the second stage the number of pains,

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

†We have called contractions during which the uterus cannot readily be indented at the height of a contraction as "good", in comparison with contractions during which the uterus is readily indented, which we have called "poor."

I would disagree with Dr. Mengert, however, upon the question of the significance of edema in the toxemia patient, not from the point of representing that edema is the cause of the phenomena of eclampsia, but to suggest that important consideration in some of the late and terminal phenomena.

When edema is present and can be reduced the severe pre-eclamptic and eclamptic seem to do much better than the patient who is not edematous. Practically all forms of treatment which we have today have as one of their purposes the reduction of tissue electrolyte, particularly sodium, and the reduction of edema. Even the speaker limits the amount of fluid intake and keeps his patients upon a high-protein and a low-salt diet.

However, in the limited state of our knowledge of this subject one cannot be too dogmatic. The amazing thing about the whole problem of eclampsia and the discussions which arise concerning it is the fact that so many different treatments, apparently diametrically opposed in one direction or another, are so successful in the hands of those who are experienced in the management of this disease.

DR. NEWLIN PAXSON, Philadelphia, Pa.—We have in our work reached the same conclusion, that angiospasm shows a pathologic change in eclampsia. We thought this might account for Stroganoff's theory that the use of an old drug which had been more or less discarded (chloral hydrate) because of fear of damage to the liver, might actually represent an approach both as a sedative and a vasodilator. Therefore, we have been using it in much larger quantities than we have used morphine, feeling that it did not produce any ill effects. And although there might be some danger of liver damage, we believe that the problem is so acute and relatively short-standing, we have used chloral hydrate as our possible answer.

As to the second point, we are following the Smiths' work in regard to a toxin being responsible for the angiospasm. I was wondering if Dr. Mengert would care to correlate any opinions he may have on the investigations of the Smiths in relation to angiospasm?

DR. MENGERT (Closing).—It was my desire to focus attention upon angiospasm and I think that desire was accomplished. There was no claim made that the kidney lesion in itself produced hypertension. I think, of course, that some kidneys do not have a great degree of angiospasm. The intensity of angiospasm varies in different parts of the body. For example, I remember well a patient who had necrosis of, and lost a large part of the right gluteus. At the time we thought it was due to thrombosis. I now believe this must have been due to angiospasm. Why there should have been angiospasm of that particular end artery no one can answer at the present time. Certainly, in the more severely ill patient, as Dr. Taylor suggested, angiospasm is a feature of the syndrome and every one who has written on the pathology of the kidney agrees with this. Fahr, in 1924, spoke of the glomerular ischemia.

Edema is present as extracellular fluid and I think the important thing we must bear in mind in treating these patients is not to bring fluid back into the vascular tree and thereby overload the circulatory system. I do not think that during the immediate convulsive stage it is of importance to worry about the edema. I think the important thing is the effect of the water. I remember a patient I had a hand in treating some years ago where we used all known procedures from hypertonic fluids to blood transfusion and finally this patient went into a stasis eclampticus and died. Now I believe she died from water intoxication. We must remember that water intoxication can produce convulsions and I would like to close on the thought that perhaps some of the convulsions we see in eclamptic patients are the result of the treatment and not of the disease.

pains required to complete this descent phase varied from none to ten. Following completion of descent, these patients then had the same pelvic floor phase characteristic of the larger group. The total duration of the second stage for this smaller group, who had both a descent phase and a pelvic floor phase, cannot logically be compared directly with the total duration of the larger group, which had only a pelvic floor phase.

TABLE II. PRIMIPARAS, DESCENT PHASE

NUMBER OF PAINS	0-1	2-4	5-10	OVER 10
Good pains	32 per cent	37 per cent	31 per cent	
Poor pains	23 per cent	42 per cent	33 per cent	2 per cent

Study of the descent phase in the 232 primiparas (Table II), showed that the descent was a bit more rapid with good pains than with poor ones but that, even with poor pains, all had reached the pelvic floor in ten pains or less. Two per cent—a total of three patients only—according to the records, showed 13, 15, and 20 descent-phase pains, respectively. In none of these three patients were the pains actually counted, but only “estimated,” and in none of the three was a vaginal examination done. Critical review of these three records would seem to indicate that only the last one of the three probably had more than ten pains to reach the pelvic floor. In the 269 multiparas (Table III), the vast majority had reached the pelvic floor within six pains, and all save two patients had reached the pelvic floor within ten pains or less. One of these two patients was “estimated” to have had fourteen contractions in her descent phase, and the other one sixteen. No vaginal examination was made in the first, and the record is uncertain as to whether a vaginal was made in the second. Assuming that the second patient did actually have more than ten pains in her descent phase, we then have one primipara out of 790 and one multipara out of 1178 who required more than ten pains to reach the pelvic floor after complete dilation of the cervix.

TABLE III. MULTIPARAS, DESCENT PHASE

NUMBER OF PAINS	0-1	2-4	5-10	OVER 10
Good pains	67 per cent	29 per cent	4 per cent	
Poor pains	57 per cent		13 per cent	1 per cent

As stated above, the pelvic floor phase of those patients having a descent phase was in no way different from the larger group, who had no descent phase. The 1174 multiparas (Table IV) were found to have completed the pelvic floor phase in the vast majority of cases in about three pains, and in virtually all instances in ten pains. Again, good pains accomplished the end result more quickly than poor pains, but the difference between good pains and poor pains was not nearly so marked as we had previously thought, further emphasizing the value of pain measurement over minute measurement. Eight patients only (less than 1 per cent of the total), according to the records, required more than ten pains. (One patient, previously delivered by cesarean section and, therefore, a primipara for purposes of this discussion, was also inadvertently included in Table IV.) Six of these eight patients were said to have had 12, 13, 13, 14, 14, and 15 pains, respectively. The duration in minutes of the second stage in these same patients was 20, 20, 24, 28, 28 and 30 minutes. In most instances, the pains were not actually counted, but the number only estimated.*

*While the house staff has been very diligent in counting the pains, it is only natural that they should forget occasionally. As a matter of fact, intern and resident usually keep separate count, and when they disagree, an estimate is the result.

instead of the number of minutes. This is very logical, since fifteen pains at four-minute intervals, thereby consuming one hour, should not logically be expected to accomplish more than fifteen pains at two-minute intervals, which would consume only half as much time. It should be noted here—somewhat parenthetically—that fifteen pains at one-minute intervals do not actually accomplish as much as fifteen pains at two-minute intervals. This is probably due to an insufficiently long period of relaxation, and might be considered as sub-clinical tetany.

In the last year and a half, since the above plan was adopted, the vast majority of our records contain the number of pains, in addition to the previous data theretofore included. Not always has the vaginal examination been made, although there has developed somewhat of a tendency to examine most patients by vagina if the head does not reach the perineum immediately after the cervix is thought to be dilated. We have not discouraged this tendency, because, in a teaching clinic, we feel it highly important to impress upon everyone that such is the normal course of events.

TABLE I. STATION AT COMPLETION OF DILATATION

NO. OF PATIENTS		ON PELVIC FLOOR		ABOVE	
		NO.	PER CENT	NO.	PER CENT
Primiparas	790	558	71	232	29
Multiparas	1178	909	77	269	23

Among 790 primiparas with occiput presentations (Table I) the head was found to be on the pelvic floor at the time the cervix was completely dilated in 558 patients (71 per cent). In 59 others, the head reached the pelvic floor either before or during the course of the next uterine contraction. In other words, the head was on the perineum at the time the cervix was dilated, or with the next pain, in a total of 617 out of 790 primiparas (78 per cent). Similar figures for multiparas showed 909 of a total of 1178 on the perineum at the time the cervix was dilated (77 per cent). One hundred sixty-four others reached the perineum on or before the completion of the next contraction. A total, then, of 1073 of the 1178 multiparas had the head on the perineum at the completion of dilation, or within one pain thereafter, (91 per cent). One cannot help but wonder whether the strictly normal course of events does not call for the head being on the perineum at the time the cervix is completely dilated. One cannot, however, reason conversely that the head on the perineum means complete dilatation, as we see a definite percentage of our patients with the head on the perineum for a considerable time before the cervix is completely retracted. Two to three per cent of all patients show this. In one group (primiparas with poor first-stage pains), 8 per cent will have the head well down on the perineum by the time there is 7 to 9 cm. dilatation.

We have previously urged² that the second stage be considered as being composed of two phases: one, a descent phase, and two, a pelvic floor phase. From the above, it is quite apparent that at least 70 odd per cent of both primiparas and multiparas have the head on the perineum at the time the cervix is completely dilated. These patients have only a pelvic floor phase in the second stage. The remaining 20 odd per cent, of both primiparas and multiparas in this present series, did not bring the head to the pelvic floor for a variable time after the cervix was completely retracted. As will be shown, the number of

required more than thirty pains. Three of these five patients were eventually delivered with forceps, and all of them required more than an hour, except one, who was delivered at the end of forty-six minutes. The incidence of forceps in this poor-pain group is as follows: of the 269 patients delivered in the first ten pains, 39 were delivered with forceps; and 17 of the 175 in the eleven to twenty pain group were similarly managed. This relatively higher rate of forceps exhibition is the result of our previously gained impression that primiparas, with very poor pains, are quite unlikely to deliver themselves spontaneously in a reasonable period of time. This present study has gone a long way toward establishing the contradiction of that idea, since 444 (less a few of the forceps cases) are shown to have delivered themselves within 20 pains or less. Of the remaining 44 patients, 39 were delivered between 21 and 30 pains, six of these by forceps. Five had more than 30 pains, and three of the five were delivered by forceps. It seems, on the basis of this study, that it is rather futile to expect a patient to deliver herself spontaneously if she has not done so within thirty pains. It should be noted, however, that the five patients having more than thirty pains in this present series constitute only 1 per cent of those having poor pains, and slightly more than one-half of one per cent of the total number of primiparas. Similarly, it might be noted that the 44 patients having more than twenty pains constitute about 5 per cent of the total number of primiparas.

Discussion

In other words, the primipara, with pains at two-minute intervals, will nearly always have delivered herself within forty minutes. The primipara, with pains at three-minute intervals, can be expected to deliver herself within one hour. The primipara, with pains at four-minute intervals, will naturally require up to eighty minutes, even if the individual pains are of good intensity.

Conclusions

1. Complete retraction of the cervix as a measure of the end of the first stage, or of the beginning of the second, leads to a better understanding of the physiology of the second stage and a better clinical judgment of its progress.

2. Measurement of the duration of the second stage by number of pains, rather than by number of minutes, is more logical and, in our hands, a much more satisfactory method of measurement.

3. Most primiparas can be expected to deliver themselves spontaneously, after the head reaches the perineum, in twenty pains or less.

4. A simple second-stage formula might be stated as follows:

All patients, primiparas and multiparas, will complete their descent phase in ten pains or less.

All multiparas will complete their pelvic floor phase in ten pains or less.

Primiparas, with good pains, will complete their pelvic floor phase in twenty pains or less. Primiparas, with poor pains, will complete their pelvic floor phase, in nearly all cases, in thirty pains or less.

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In at least three of the six patients, no vaginal examination was done. In three cases, the pains were said to be one to one and one-half minutes apart, which, as noted above, is not a desirable situation. It seems doubtful whether any of these six patients had materially more than ten pains in her pelvic floor phase. The remaining two patients certainly had more than ten pains.

TABLE IV. MULTIPARAS, PELVIC FLOOR PHASE

NUMBER OF PAINS		0-3		4-6		7-10		OVER 10	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Good pains	602	470	78	100	17	31	5	1	0
Poor pains	572	386	67	135	24	43	8	8	1

One, a twenty-five-year-old gravida ii, para i, had the head on the perineum three minutes after completion of dilation (one pain), and delivered spontaneously thirty-six minutes later, after eighteen pains. She was normal in all respects; the baby weighed 3,640 Gm.; and the head was completely rotated at the time the head reached the pelvic floor. She was said to have had "very poor" pains. She had been given 2.5 mg. of Pontocaine in 0.5 c.c. of 10 per cent glucose intraspinally. We do not feel that this minimal dose saddle block materially reduces the effectiveness of second stage pains, but, like any other anesthetic, it does have some effect. The other patient, a thirty-year-old gravida ii, para i, required thirty-five minutes (ten pains) to reach the pelvic floor, at which time the head rotated posteriorly and was delivered after twenty-nine very poor contractions with the aid of low forceps. (It should, perhaps, be stated here that forceps were used only five times in the delivery of the 1174 multiparas). According to this patient's history, this pregnancy terminated at the end of thirty-three weeks, and the attendant was quite surprised to find the baby weighed 3,100 Gm. This was quite readily explained, however, when it was noted that the placenta weighed 780 Gm. The infant did, throughout the neonatal period and for a considerable time thereafter, react like a premature infant—required incubator care, etc. While it is, therefore, possible for a multipara to require more than ten pains to deliver the baby over the perineum, it is of rare occurrence in this present series.

TABLE V. PRIMIPARAS, PELVIC FLOOR PHASE

NUMBER OF PAINS		0-10		11-20		21-30		OVER 30	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Good pains	302	242	80	60	20				
Poor pains	488	269	55	175	36	39	8	5	1

The survey of the pelvic floor phase in primiparas also produced very interesting data. Three hundred two of these primiparas (Table V) were said to have good second stage pains. Two hundred forty-two (80 per cent) of these were delivered within ten pains or less. The remaining 60 (20 per cent) were delivered in most instances in fifteen pains or less, and in all cases within twenty pains or less. Only five of the 302 patients had forceps deliveries, thus reflecting our previously gained confidence that primiparas with good pains will promptly deliver themselves spontaneously. Two of these five forceps cases might have had a few more than twenty pains had the forceps not been used. One can, however, say very confidently that all primiparas, with good pains, will deliver themselves over the perineum in twenty pains or less.

Four hundred eighty-eight primiparas were said to have poor second-stage pains. A little more than half of these patients were delivered in ten pains or less. Another thirty-six per cent were delivered in the second ten-pain period. Eight per cent required twenty-one to thirty pains, and 1 per cent—5 patients—

A large series of healthy, native-born American women in good nutrition and condition, with no pathologic processes, would probably deliver themselves spontaneously in a manner equal to the series Dr. Calkins has reported. But I think we would find in an extensive practice of mixed nationalities, fearful of labor, elderly so far as the first pregnancy is concerned, and demanding and receiving many of the widely prevalent methods of sedation or anesthesia, that their necessary effort to complete the second stage would come far beyond the number of pains in Dr. Calkins' series. I would be interested to know if Dr. Calkins regards the women who had more than thirty pains in the pelvic-floor phase to have had secondary inertia, and if any of his patients could be considered as having had primary inertia.

If we must examine a woman vaginally to determine complete retraction of the cervix as a determination of the physiologic end of the first stage, which is an excellent suggestion, we will probably have a large increase in the number of vaginal examinations to determine the progress of labor, but if we adopt the formula suggested we may not have as many forceps deliveries as are practiced in many clinics.

DR. RUDOLPH W. HOLMES, Charlottesville, Va.:—In 1893, Kroenig and Ries independently wrote articles which extolled the merits of rectal examinations in labor. The history of rectal examinations is an interesting one. Textbooks and journal pages gave scant publicity to their advantages, so that from 1893 to 1915 there was not one formal paper on the subject. Yet, the procedure became a near routine throughout the world without the aid of publicity; its growth was insidious. I wrote a paper in 1915 on the advantages of rectal examinations, based entirely upon my experience as a routine in my own work, and as a method required by my subordinates in various hospitals. To the latter, a vaginal examination was barred except on a special permission.

I do not believe I am prejudiced in its favor—I merely express an opinion based upon my own experience. I still believe that rectal examinations will elicit all needful information in the vast majority of cases; when a failure does occur, usually it will be found that the findings from a vaginal touch will be equally futile; when this does happen, manual examination through the vagina may be imperative. I believe that most antagonists to the method have not given the method a full trial. Abdominal palpation and rectal touch are without danger; vaginal examinations do carry a menace from infection. I express myself strongly as the essayist reflects an unfortunate retrogressive trend as regards methods of investigation.

DR. CALKINS (Closing).—Of course, this was not a paper on the first stage of labor and therefore did not deal with the retraction of the cervix. It was not a paper on anesthesia but these patients did have some form of analgesia as well. Too much anesthesia will prolong labor, it should be stated—both first and second stages—and where we have used too much anesthesia a longer labor has been the result.

This was not an attempt to substitute vaginal for rectal examinations. I quite agree that up to the final stages of dilatation the patient may be very properly and appropriately handled by means of rectal examinations, but my point was that in many instances the cervix is thought to be properly dilated when it is not and I believe a vaginal examination is less dangerous than forceps delivery.

Discussion

DR. ROBERT A. ROSS, Durham, N. C.—In a recent study at Duke University a listing was made of the number of pains rather than judging labor in terms of hours or minutes. The results are in accord with Dr. Calkins' observations. We have long held the thesis that, perhaps, the best way to teach obstetrics is to have the student sit by the laboring woman's bedside with his hand on her abdomen. In this way, he can judge not only the duration, and interval of the pains, but also their intensity. From the observations of Rucker, Murphy, and Torpin, we know that pains may not be productive. They also showed that the rest period between pains was just as important as the pain itself. The essayist has re-emphasized this point. We must also recall the behavior of the uterus in prematurely induced labor as compared to normal labor.

Another point is the inability to judge the dilatation and, more important, effacement of the cervix by rectal examination alone. Surely, in our efforts to teach asepsis, we do not examine our patients by the vagina often enough to evaluate properly the behavior of the cervix. Too often when the patient is on the delivery table and asleep, only a thin or not completely dilated cervix is present. The essayist properly calls for an examination by vagina whenever the patient has not brought the baby to the vulva after a period of hard pains. He also distinguishes between a patient who has the fetal head well in the pelvis, without pain, when the labor may be inordinately long and perplexing, and the patient who starts labor with the head unengaged and carrying on in fine fashion.

The incidence of forceps delivery is noteworthy and no doubt springs from listing the number of pains rather than time of labor. Several years ago we had our resident in a general hospital, list the time of day, or night, of all forceps deliveries. The result was as expected. The tired, harassed doctor delivered more patients by forceps before mealtime, bedtime, nad office-hour time than at any other. The essayist's observations should help in anticipating the time of birth.

DR. PHILIP F. WILLIAMS, Philadelphia, Pa.—Dr. Calkins' studies of the progress of labor which he has presented in recent years have been of much interest. In the present essay he has offered us a very simple rule by which one can measure numerically by contractions the degree of effort needed to bring about descent and expulsion of the fetus. It might seem worth while to substitute the formula which he has derived from a fairly large sampling of patients for the time-honored formula of two hours in what we have regarded as the second stage, or thirty minutes with the head on the perineum and no progress, to indicate the necessity for artificial delivery.

I am uncertain, however, as to whether this group of nearly 2,000 women represents a selected group of consecutive cases. No mention has been made of borderline cases. Again, the age of the patient or physical condition, the size of the baby, and the fetal position do not seem to have occasioned any delay. All these factors would seem to occasion more marked variation from the conclusions as to the muscular effort required for descent and expulsion. The incidence of forceps deliveries in the group reported is indeed quite low.

Dr. Calkins' indication for making a vaginal examination is excellent. Certainly, rectal examinations are inconclusive in many instances in determining if the cervix has retracted over the head. The ease of rectal examinations and the avoidance of preparation of both patient and physician and a possible slight increase in morbidity in vaginal examinations possibly make us a little lazy in determining the exact state of the cervix. Very often when the cervix is felt by rectal examination to be fully dilated and then vaginal examination is made we find a very thin cervix, 6 or 8 cm. dilated and probably having very little muscular fiber in it. In reality, the muscular cervix has retracted over the head and the thin mucous membrane layer is still present and retracts on almost the slightest stretching or pushing. The obstructing anterior cervical lip, when pushed over the head and held there during one pain, is often followed by almost immediate delivery.

Gross Fetal Mortality.—In consulting the literature, six authors gave as gross fetal mortality all stillbirths and neonatal deaths occurring from the twenty-eighth week of pregnancy to term. These mortalities varied from 11.5 per cent¹ to 35.3 per cent.²⁹

In our cases for the five-year period 1933-1937, among 773 breech deliveries, there were 244 stillbirths and neonatal deaths, 31.6 per cent. The vast majority occurred among very immature babies, although a considerable number were dead on admission or had malformations incompatible with life. For the five-year period 1942 to 1946, there were 51 deaths among 467 deliveries of breech cases, 17.4 per cent.

Corrected Fetal Mortality.—Since it is obvious that a considerable number of deaths occurring in the gross rate cannot be attributed to the presentation, deductions have been made in order to determine the fetal mortality due to the presentation itself. It, therefore, seems reasonable to deduct (1) nonviable prematures (less than 1,500 Gm., 3 pounds, 5 ounces), (2) babies with fatal malformations, and (3) those who were already dead on admission. Correction by deduction for deaths due to prolapsed cord and to maternal complications, however, seems indefensible. Whether or not twin pregnancy, with one or both fetuses presenting by breech, should be deducted or included has been debated in the literature. Actually, this is of little importance since the small number of multiple pregnancies would have little statistical effect. We have included only cases in which the first twin presented by breech and considered it as one case.

With the above corrections, eight reports reviewed showed mortality rates of 5.38 per cent³³ to 22.7 per cent.⁷ Our mortality for the 1933 to 1937 period showed 53 deaths in 538 cases, or 9.9 per cent, and for the 1942 to 1946 period was 30 deaths among 446, or 6.7 per cent.

Corrected Premature Mortality.—It is a fairly common belief that breech presentation is especially dangerous for the premature child. This danger has been ascribed to the chance of delay in delivery of a relatively large head through a birth canal inadequately prepared by the small body and shoulders. This has probably been too much emphasized by the inclusion in many reports of very immature fetuses who would have little chance to survive with any presentation. If we arbitrarily assume, as is customary, that birth weights between 1,500 Gm. (3 pounds, 5 ounces) and 2,500 Gm. (5 pounds, 8 ounces), for babies alive on admission and having no gross developmental defects, represents viable prematurity, we were able to find in the literature mortality rates varying from 14.3 per cent to 48.6 per cent.^{32, 33, 36} Morton³² also states that the general mortality for all premature babies in his hospital was 36.8 per cent. In our group of such babies there were 145 with 37 deaths, 24.1 per cent. Forty-five weighed less than 4 pounds, with 42.6 per cent mortality; 58 weighed between 4 and 5 pounds, of whom 19.3 per cent died, and 42 weighed over 5 pounds but less than 5 pounds, 8 ounces, with 10 per cent deaths. If it is remembered that our figures include both stillbirths and neonatal deaths, there is apparently no indication of a definitely increased risk for viable prematures presenting by breech. In this connection, with very premature babies (3 pounds, 5 ounces, to 4 pounds) it is interesting to note that the mortality rate for the first five-year period (1933 to 1937) was 55 per cent and for the last five-year period (1942 to 1946) was 37.5 per cent, due, we believe, to better premature care in the later group.

Corrected Term Mortality.—Variations of opinion as to what constitutes a full-term fetus have given rise to considerable confusion in the literature as to the interpretation of results, and, at times, to false conclusions. Some authors apparently relied on the questionable estimate of maturity from the reported

FETAL MORTALITY IN BREECH DELIVERIES*

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IT IS commonly thought that breech presentation, while having little effect upon maternal mortality, and small effect upon maternal morbidity, definitely increases the danger to the fetus, and that this added risk over vertex presentation is due largely to asphyxia and birth injury. The fact that the birth of the child must occur within a few minutes after expulsion to the level of the umbilicus, or compression of the cord may occur, also often results in birth injury from efforts on the part of the obstetrician to overcome dangerous delay in delivery.

There are also other hazards to the fetus, information about which has not been so widely disseminated. In order to gather more data as a background for better management, we have reviewed the recent literature and studied a moderately large group of breech cases occurring in 25,532 deliveries, during two five-year periods, 1933 to 1937, and 1942 to 1946.

The commonly reported incidence of breech presentation is from 2.1 per cent²³ to 6.32 per cent.³⁶ In our group of 25,532 deliveries, breech presentations occurred in 1240, or 4.8 per cent. At variance with the usual statements relative to etiological factors, pelvic contraction, as an obstacle to engagement of the vertex, seemingly has little or no effect in the production of breech presentation. Pelvic contraction occurred in only 2.7 per cent, actually a rather low incidence. In our experience, other commonly stated causes, such as placenta previa and the toxemias, are important only as a cause of premature labor. We were able to find no statistically discernible cause for breech presentation other than prematurity and twin pregnancy.

Vartan⁵⁷ asserts that the reason why breeches persist until term is not to be sought in factors which prevent the head from engaging but are those which prevent spontaneous version from taking place and believes that extension of the legs is a prime factor, by giving the fetus an extended attitude.

Fetal Mortality

It is generally conceded that breech presentation entails more danger to the fetus than does vertex, but there has been considerable disagreement as to the exact degree of this added risk. There is also some debate as to the parts played in this increased mortality by the presentation itself and by other factors which might be the cause of the presentation. In an attempt to arrive at an answer to the question, different calculations have been used which make comparisons difficult and have led, at times, we believe, to doubtful conclusions. A common error has been the acceptance of the gross or total fetal mortality as representing the percentage risk for all groups of breech presentations.

*Read, by invitation, at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

TABLE II. MORTALITY RATES AND BIRTH WEIGHTS

	5 LBS. 8 OZ. TO 5 LBS. 15 OZ. PER CENT DIED	6 LBS. TO 6 LBS. 15 OZ. PER CENT DIED	7 LBS. TO 7 LBS. 15 OZ. PER CENT DIED	8 LBS. TO 8 LBS. 15 OZ. PER CENT DIED	9 LBS. AND OVER PER CENT DIED
Primiparas	14.8	7	1.4	16.7	50*
Multiparas	6.1	1.4	3.4	7.9	17.9
All cases	10.0	4.4	2.5	11.3	20.0

*Only 2 cases.

Frank Breech.—In previous studies, Siddall and I^{52, 53} drew attention to the fact that several authors have expressed the belief that there is a higher fetal mortality associated with frank breech deliveries. In our first group of cases, 1933 to 1937, we were unable to confirm this and even stated that, in our experience, after grouping as to parity and further subdivision as to premature and term babies, there was without exception a *lower* mortality for frank breech.

In our 1942 to 1946 cases with viable babies, I am unable to confirm a lower death rate for frank breech except for premature primiparas and term multiparas. For premature primiparas, the fetal death rate was 12.5 per cent for frank breech and for other breech presentations, 14.2 per cent. For term multiparas, the percentage was 0.0 for frank breech and for other breech presentations, 3.5 per cent. It would seem, therefore, that frank breech is associated with little if any added risk, to the fetus.

Parity.—Statements in the literature vary considerably in regard to parity as a factor in fetal mortality, although it might naturally be expected that they would ascribe a higher rate for primiparas. And this seems to be borne out by the available data. Nevertheless, King and Gladden²² report mortality rates of 7.7 per cent for primiparas and 12.5 per cent for multiparas, for babies weighing over 5 pounds. They offer in explanation the fact that dead babies in this group averaged 1 pound, 4 ounces heavier when born of multiparas.

Our experience is shown in Table III.

TABLE III. STILLBIRTH AND NEONATAL MORTALITY RATES FOR VIABLE BABIES OF PRIMIPARAS AND MULTIPARAS, 1933 TO 1937 AND 1942 TO 1946

TOTAL MORTALITY		PREMATURE MORTALITY		TERM MORTALITY	
PRIMIPARAS (PER CENT)	MULTIPARAS (PER CENT)	PRIMIPARAS (PER CENT)	MULTIPARAS (PER CENT)	PRIMIPARAS (PER CENT)	MULTIPARAS (PER CENT)
5.7	7.8	13.8	31.9	4.7	3.4
		1942 to 1946			
3.1	5.0	13.3	31.0	1.5	1.4

An interesting and surprising finding is the high mortality of premature babies of multiparas. This has been noted elsewhere in the literature.¹ It seems obvious that this is responsible for a reversal of the relative results for the combined and for full-term deaths. A partial explanation can be found in the greater proportion of large prematures (5 pounds to 5 pounds, 7 ounces) delivered by primiparas, 40 per cent as compared to 23 per cent by multiparas. It is also possible, as term babies are larger in multiparas, that premature babies of the same weight might actually be less mature and therefore more likely to die.

Length of Labor.—There is little evidence in the recent literature^{2, 12, 24, 27, 37} to support the belief that breech labor is likely to be prolonged with adverse effect upon the fetus. In our groups, the average length of labor for women whose babies weighed 5 pounds, 8 ounces and over and died, was 20 hours, 15

last menstrual period. Others made no mention of, or were too indefinite concerning, size and maturity. The majority of authors, however, agreed that a fetus weighing 2,500 Gm. (5 pounds, 8 ounces) or over is mature insofar as its ability to survive is concerned. We have reviewed ten reports in which the results for term babies were computed by this criterion (with deduction for gross malformations and fetuses dead on entrance). There was considerable variation in results, especially where small numbers of cases were concerned. Mortality rates for 200 cases or more varied from 8.5 per cent⁴ to 12.5 per cent.¹⁷ Our stillbirth and neonatal mortality in both groups of cases (1933 to 1937, 1942 to 1946) was 42 deaths in 800 deliveries, or 5.2 per cent.

TABLE I. COMPARATIVE FETAL MORTALITY (FOR VIABLE TERM BABIES)

	GENERAL FETAL MORTALITY (PER CENT)	BREECH MORTALITY (PER CENT)
1933 to 1937	1.8	6.5
1942 to 1946	1.1	3.5
Both periods		5.2

Special Factors in Breech Mortality

Prolapse of the Umbilical Cord.—Authors reporting the incidence of prolapsed cord vary in percentages from 0.9⁴² and 11.9.³⁵ Among a total of 5822 cases of breech in the literature reviewed, this complication occurred in 2.9 per cent. Among our 984 cases with viable babies, the cord prolapsed 31 times, or in 3.2 per cent. Caldwell and Studdiford³ gave an incidence of 0.5 per cent in 6947 cases for all positions, and this is close to the accepted average. It is apparent, therefore, that prolapsed cord in breeches is about six times that for all presentations.

The importance of prolapsed cord in relation to fetal death in breech presentations, then, is evident. In 159 cases reported by seven authors, there were 68 fetal deaths, about 43 per cent. So definite is the fetal danger that Studdiford³⁹ and Sherman³⁸ strongly advise routine vaginal examination on rupture of the membranes in order to be immediately aware of the complication. In our 31 cases there were 10 deaths, or 12 per cent. In other words, approximately 3 per cent of the cases with prolapsed cord are responsible for 12 per cent of the total mortality.

Contracted Pelvis.—The danger to the fetus, with contracted pelvis, is recognized throughout the literature. Particularly dangerous are the mild contractions which are frequently overlooked, with disastrous results. As yet, there seems to be no adequate method which provides a comparison of the size of the fetal head in the fundus with that of the pelvis. The existence of cephalopelvic disproportion, then, is often not discovered until late in the second stage of labor, when the child is seriously endangered from asphyxia or from urgently indicated attempts at delivery. The seriousness of the complication as a factor in breech presentation is evident from various reports.^{3, 5, 12, 17} As an example, Gordon, Garlick, and Oginz¹⁷ found a 31.7 per cent fetal death rate in primiparas and 32.6 in multiparas. In the material here reported, we found 22 contracted pelvises (2.7 per cent of term cases), of which 70 per cent were delivered by cesarean section. There were no fetal or maternal deaths.

Birth Weight.—The weight of breech babies we believe to be an important factor in mortality rates. Most writers are in agreement that large babies presenting by breech have a high death rate. Mohler^{29, 30} reports that 50 per cent of primiparous breech babies weighing 8 pounds or over, died. Experience of others also shows that there is a higher-than-average death rate from small, but viable babies. The best results are obtained with babies of medium weight.^{7, 16, 52} Our result in the first group of cases would tend to confirm this:

other objections. This apparently is slight, when done gently and without anesthesia, as shown by preponderance of evidence in the literature, seventeen out of twenty-one authors recommending it.

External version, however, is not universally successful, especially if done early. Vartan⁵⁰ states that breech presentation is common until the 34th week, so common that it must be regarded as a normal occurrence at certain stages of pregnancy, and found 680 spontaneous conversions to vertex among 1000 cases after the thirtieth week. The majority of these had occurred by the thirty-fourth week, although 28 were spontaneously converted to vertex in the thirty-fifth and thirty-sixth weeks. Spontaneous version is rarely followed by reversion to the original breech (only 5 per cent) while Ryder⁵⁵ finds that reversion occurs in 33 per cent of external versions. There is a tendency for a higher percentage to reconvert if they are done early, while, after the thirty-first to thirty-second week, this tendency diminishes. External version then, while technically easy, is not universally successful, but we believe deserves an adequate trial in an effort to lower fetal mortality from breech presentations.

Cesarean Section.—It is well to recognize at the beginning of any discussion of cesarean section for breech cases, that it has, with few exceptions, a fetal indication only. We have stated before, and are borne out by the literature, that there is very little, if any, added maternal risk from breech delivery. There is, however, a definite added risk to the mother from cesarean of from three to ten times that of vaginal delivery. It also carries with it possibilities of trouble in future pregnancies. The subject then resolves itself around the question as to what degree of fetal danger permits an added maternal risk, by abdominal section, for its relief. We have shown, I think, that, in at least three groups of cases, there is so great fetal loss that cesarean should be considered if prophylactic version fails.

Contracted pelvis, even in the very mild degrees, is especially dangerous to the child presenting by breech. As mentioned before, we have found no reliable method of estimating disproportion with the head in the fundus. Therefore, we think that delivery by cesarean section is indicated from the fetal standpoint whenever any degree of disproportion seems probable. In our twenty-two full-term cases, section was done in fifteen and no babies or mothers died. We realize that it is impossible to draw conclusions from so small a group of cases, but our results are apparently different than those found in reports where a high percentage of sections was not done.

As noted before, fetal mortality is high in primiparas over 30 years of age, and particularly so after 35 years. In the primiparas over 35, there is frequently such a great desire for a living child as at least to merit consideration of delivery by section. We believe that the prospective parents, after explanation of the relative fetal risks, should have a voice in the choice of procedure.

From data previously presented, birth weight appears to be an important and frequently overlooked factor in fetal mortality. Babies of medium weight show only a moderately increased mortality, but for larger babies (8 pounds and more) the rate becomes excessive, particularly for primiparas. We realize that there is no accurate method of estimating the size of the unborn child, but we can usually classify the fetus as large, medium, or small. Should the size be large, in the interest of the child and from all evidence collected, we believe that careful consideration should be given to delivery by cesarean section, particularly if the patient is a primipara.

It is evident that combinations of two or more of these factors make section more likely to be the procedure of choice.

Early Breech Extraction.—As early as 1926, Irving and Goethals²¹ reported a reduction of fetal mortality in breech presentation by the use of routine breech extraction as soon as the cervix was completely dilated and Goethals^{15, 16, 45, 46, 48}

minutes. There were two cases of much-prolonged labor due, apparently, to primary inertia that contributed to this average. Without these two cases, the average length of labor was 12 hours, 20 minutes. From the data available, it is questionable that breech presentation, in itself, is associated with sufficient prolongation of labor to be a factor in fetal mortality.

Age of Primiparas.—We have always felt apologetic when using the term “elderly primipara,” especially when applied to women in their thirties, as an indication for various obstetrical procedures. Nevertheless, the literature^{2, 4, 17, 42} and our own experience show an increasing death rate for breech babies of these women; and this is especially true if the babies are large. From 1933 to 1937, for term babies of primiparas over 30 years, the mortality was 13.3 per cent compared to 6.8 per cent for the younger group. In our 1942 to 1946 group, the death rate was 10.5 per cent for primiparas of 35 years or more, as compared to 5.8 per cent for those under 30.

Early Rupture of the Membranes.—We have been unable in the material at hand to show any increased fetal risk for dry labors with breech presentation. There seemed to be the same accelerating effect on labor, insofar as we could judge, due to early rupture of the membranes, that has so frequently been observed for vertex presentations. In our opinion, the increased risk is due to the danger of prolapse of the cord with early rupture of the amniotic sac, rather than to any effect upon labor.

Skill of Attendant.—It has been said that there is “no substitute for experience” and this dictum holds true, we believe, in the management of breech cases. In previously quoted figures in this report, we have shown increasingly better net fetal death rates in later years. In the first series, 1933 to 1937, approximately two-thirds were delivered by internes and residents in training, with the usual supervision. In the 1942 to 1946 group, at least 95 per cent were delivered as private patients by a staff composed largely of diplomates of the American Board of Obstetrics and Gynecology.

Other factors affecting the net mortality rate were the same for both groups. Pertinent to this is Dieckmann’s statement⁶² that his corrected mortality rate for term babies is 4.2 per cent and Tomkins’ report⁵⁶ of 2.7 per cent net mortality in a group of patients, all of whom were delivered by Board members. The fact remains, however, that breech delivery, in any hands, is associated with a higher-than-average fetal mortality.

Treatment

It is not necessary, we believe, in a study of this kind to give detailed management of breech presentation during labor and delivery. While we do not intend to ignore the value of proper management, this can be found in all textbooks and in numerous papers. There are, at times, interesting new approaches being advocated and several of the older procedures might well be re-examined. Among these are:

Prophylactic External Version.—As we have shown that breech presentation, even with expert management, is associated with an inevitably increased fetal risk, it becomes obligatory at least to consider prophylactic external version for conversion to a more favorable position. This procedure has been objected to on grounds of the risk involved, which might arise from separation of the placenta and from entanglement of the umbilical cord; and on the grounds that there is a certain percentage of failure or reconversion back to the original breech presentation. The degree of risk involved, of course, far outweighs all

Prophylactic version as a method of reducing breech mortality, we believe, deserves more universal consideration.

Elderly primiparas, cases with pelvic contraction, even though of mild degree, primiparas with large babies, and cases with various combinations of these conditions deserve careful consideration of delivery by cesarean section.

Better care of prematures should help reduce mortality among those developed sufficiently to survive extrauterine life.

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has continued the discussion in subsequent publications. He states that extraction is undertaken after, but not necessarily immediately after, attainment of full dilatation with respect to the breech, and indicates that stillbirths and neonatal deaths have been reduced 50 per cent by this policy, his personal rate being 2.3 per cent. Potter, Erving, and Brown⁶⁰ believe that no patient with breech presentation, after complete dilatation of the external os, should be allowed to proceed into the second stage of labor. On the other hand, Caldwell and Studdiford,³ after a trial, opposed routine extraction.

We have been reluctant to adopt the routine procedure and have resorted to breech extraction only when indicated. However, indications have been broadened considerably and, at different periods covered by this report, from 35 per cent to 65 per cent of cases have been delivered by breech extraction. We believe that further trial by experienced obstetricians is indicated.

Episiotomy.—In our experience, maternal morbidity in breech presentations can be expressed largely in terms of severe perineal damage and we believe almost routine episiotomy is indicated, not only for the benefit of the mother, but also for the protection of the fetal head and brachial plexus.

Care of Prematures.—Until more is known in regard to the *prevention* of prematurity, more attention to the care of the premature infant, in special nurseries, by trained personnel, will help to lower mortality in this large group of cases.

Summary

The fetal risk in breech presentations is more than with vertex, even in expert hands.

The maternal risk is not increased, and mortality can be explained by associated conditions not concerned with the position of the fetus. Slight increase in maternal morbidity is largely the result of a higher incidence of severe perineal injuries which can usually be prevented by episiotomy.

The very high gross fetal death rate is to a great extent due to the inclusion of very premature infants who would have little chance of survival with any position, of those having severe malformations, and of those who are already dead on admission.

We are unable to find an increased risk for viable prematures when presenting by breech.

Stillbirth and neonatal mortality for term babies is for 1933 to 1937 6.5 per cent, for 1942 to 1946, 3.5 per cent.

There is a definitely added risk to breech babies from prolapsed cord which occurs about six times as frequently as in vertex positions.

Birth weight is an important factor in fetal death for breech babies. Babies of medium size have the best chance of survival when delivered vaginally.

Although it is thought by some authors to be associated with a definitely higher death rate, we were able to show very little, if any, higher mortality for frank breech.

Increased length of labor is not a factor of importance in a higher death rate.

Babies of elderly primiparas with breech presentation have a high mortality rate if delivered vaginally.

is a poor subject for a breech delivery. His fetal death rate in this group was twice that of the young primipara. His figures also show that results are better when the breech delivery is conducted by experienced operators. Nowhere in obstetrics do skill and judgment show to better advantage than in the management of breech presentations.

In the practical management of breech delivery, I am glad that Dr. Seeley emphasized episiotomy. Too much emphasis cannot be put upon this. It should be done in every case. The incision should be wider than you think is necessary and even then it will frequently be too small. This is especially likely to be so if you follow the plan of delivering the baby soon after the cervix is fully dilated. If the birth canal has been properly prepared, the baby should roll out with the gentlest of guidance. Sometimes the cervix will close down on the aftercoming head. When that happens, it is easier to push the cervix up over the head with your fingers than it is to push or pull the head through the cervix. I have never seen this maneuver described, but it has served me well for years.

As to prophylactic version, much can be said on either side. Kellogg lists external version among the causes of premature separation of the placenta and Gibberd in a recent article says that there is no correlation between the force used and the amount of hemorrhage, nor between the amount of hemorrhage and the prognosis for the fetus.

I have studied recently the deliveries for the past four years in the Johnston-Willis Hospital (Richmond, Va.), and the ones that I and my associates had conducted in the same period elsewhere. There were 4,848 deliveries with 223 breech presentations or 4.6 per cent. The gross fetal mortality was 16 per cent. Thirty breech presentations were in twin pregnancies. There were 193 breech presentations in single pregnancies, and of these 31 babies were lost. Twenty fetuses measured less than 40 cm. In other words, 20 mothers did not reach the stage in which external version is even considered. Eleven were possible candidates for external version. Of these candidates, four had babies measuring 41, 42, 42, and 46 cm. total length, and weighing less than 2,500 Gm. Had external version been attempted on these mothers, the question would naturally have arisen, did the manipulation cause the premature labor? Two mothers were toxie and had stillborn infants, and it was thought that the result would have been the same regardless of the method of delivery. There were two cases of hydrocephalus and one of these in addition had a spina bifida. In one case there was a prolapsed, pulseless cord when the patient was first seen, and the baby was macerated. In the two remaining fetal deaths hemorrhages into the suprarenal capsule occurred. Since this lesion is twenty-two times more frequent in breech deliveries than in cephalic presentations, it is fair to say that it would have been better had these babies been turned prophylactically. On the other hand, among the 4,848 cases, there were eight external versions. One of these babies had convulsions but apparently recovered completely. One baby was lost. The mother had a bicornate uterus. External version was performed twice. Two days after the second version the mother had a hemorrhage. Shortly afterwards she went into labor and had a stillborn infant measuring 48 cm. There was a low-lying placenta. Whether the manipulation caused the bleeding or not, I cannot say. Had I been wise enough to have done an external version on the two cases that had hemorrhages into the suprarenal gland and to have refrained from doing it on the patient who proved to have a bicornate uterus, I might have saved three babies.

I believe that external version is especially indicated when there is any question of disproportion. If the head can be gotten into or above the superior strait, you can better judge the relative size of the fetal head and the maternal pelvis. Roentgen-ray mensuration of the fetal head when it is under the mother's ribs is apt to be very misleading. Someone has suggested that the mother be x-rayed in the prone position so as to bring the head as close to the film as possible. I have had no experience with such a posture, but I do know that a picture with the mother in the supine position is worse than useless.

In conclusion, I would like to ask Dr. Seeley why there were so many more breech cases in his first series than in his second? In 1933 to 1937 there were 773 breech deliveries and in 1942 to 1946 there were only 467. Has he found a way of decreasing the number of premature deliveries? If he has, that would be, to my mind, the most valuable part of the discussion.

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Discussion

DR. M. PIERCE RUCKER, Richmond, Virginia.—In the middle trimester of pregnancy, the fetus commonly presents by the breech; consequently, if the patient goes into labor prematurely, breech presentation is frequent. At term, the majority have rotated to a cephalic presentation, unless there is something that prevents spontaneous version. Hydrocephalus and major deformities of the fetus and various degrees of double uterus are common causes of breech presentations. Way, of Newcastle-on-Tyne, is of the opinion that the müllerian ducts fail to fuse completely into a normal single uterus in over 1 per cent of patients and that this is a common cause of malposition. One can see then that breech delivery must carry a high gross fetal mortality, since many fetuses are premature, many have deformities that are incompatible with continued life, and many are born by imperfect uteri. What is the actual hazard of breech delivery, is an important question which Dr. Seeley has undertaken to answer from his experience at the Harper and the Herman Kiefer Hospitals and from a review of the recent literature on the subject. After the prematures, the babies with deformities incompatible with life, and those who were dead before labor began were eliminated, there was a mortality of 3.5 per cent in his five-year group, 1942 to 1947. He is to be congratulated on this low figure, but low as it is, it is 2.4 per cent higher than his general fetal mortality for the same period. In analyzing the causes for this difference, he found that prolapsed cord accounted for 12 per cent of the total mortality. This accident occurred 31 times in 984 cases with viable babies, or 3.2 per cent. When I first read this, I thought that the frequency of prolapsed cords was unusually high. I find, however, that in the past five years I have had eight prolapsed cords in breech cases, which is slightly less than 4 per cent. It just goes to show that impressions are often wrong. In only two instances did the accident have any influence on the fetal outcome. I was surprised to learn that a viable premature had as good a chance of survival in a breech delivery as in a cephalic. My impression was to the contrary, but then again my impression might be wrong. I did not have time to check this one.

The hazard of a breech birth through a contracted pelvis is a well-recognized one. However, it plays no part in Dr. Seeley's series, as there were only 22 patients with contracted pelvises and he delivered 70 per cent of them by cesarean section. He had no deaths in this group.

I was quite interested in his table showing the mortality rates in relation to birth weights. Of the babies who weighed between 5½ and 6 pounds, 10 per cent were lost. Of the 6-pound babies, 4.4 per cent were lost, as contrasted with 2.5 per cent of the 7 pounders. When, however, the baby weighed 8 pounds, 11.3 per cent were lost and, of the 9 pounders, 20 per cent were lost. My experience is in accord with this finding.

At the first American Congress of Obstetrics and Gynecology, the subject of breech deliveries was assigned to me. At that time I charted the babies by total length. The fetal loss fell as the total length approached 50 cm., only to rise sharply in the small group of postmatures. Dr. Seeley's experience confirms the general belief that the elderly primipara

tions, 220 extractions for breech presentations and 20 extractions following internal podalic version, 3.3 per cent. These were all single breeches, the breech extractions in twin pregnancies being eliminated.

In this series, the shortest primiparous labor was two hours, the longest thirty hours, and the average thirteen hours and 39 minutes. A primipara, 42 years of age, was delivered of a 6 pound, 12 ounce infant, presenting by the breech, after a six-hour labor.

The method of delivery is of great importance in minimizing fetal mortality. We believe that deep surgical anesthesia, a deep episiotomy, a scrubbed assistant, a vaginal speculum to create an airway to the baby's mouth, and the Piper aftercoming head forceps, all play a prominent role in the management of these cases. At the Carney Hospital, we leave our cases to their natural course as long as progress is being made and interfere only when the opposite obtains. In the 220 cases of breech presentation under study, during a ten-year period, cesarean section was performed 13 times, or in 5.9 per cent.

This group of cases, consisting of single breeches in infants of 26 weeks or over, shows that fetal mortality was represented largely by stillborns, prematurity, and non-preventable causes. The highest mortality occurred among premature infants, intracranial hemorrhage being the major cause of death in this series.

There were 27 fetal deaths in the 240 breech extractions, 11.2 per cent. If we eliminate from these 27 deaths, 3 stillborns, 3 monsters, 2 macerated fetuses and 3 fetuses with congenital defects, a total of 11, there remain 16 fetal deaths, or a corrected fetal mortality of 6.6 per cent.

DR. JOSEPH L. BAER, Chicago, Ill.—It takes courage and skill to undertake the transmutation of statistics into an interesting presentation. Dr. Seeley has accomplished this well. I desire to present some statistics from the Michael Reese Hospital.

Covering a period of fifteen years, we had a total of almost 28,000 deliveries, with an incidence of breech, including all types of infants, of 3.4 per cent. Eliminating all infants under 2,500 Gm., twins, monstrosities, etc., we have a percentage of 2.4.

In the primigravida group, the first stage of labor was under twelve hours in 58.5 per cent and the second stage averaged an hour and twenty minutes. In the multiparous group, the first stage was less than twelve hours in 82 per cent. The second stage averaged only twenty-seven minutes.

The incidence of 2.4 per cent represents 592 breech presentations. Of these, 443 (75 per cent) were frank breech presentations. This is a much higher incidence of frank breech than I had realized.

Analysis of the type of delivery is as follows: in the primigravida group, 185 were spontaneous, with manual aid, 160 were by extraction, and 58 were delivered by cesarean section. In the multiparas, 151 were spontaneous with manual aid, 96 were by extraction, and 16 were delivered by cesarean section. Of the total of 74 cesarean sections, 39 were done because of the breech and 35 were done for other indications. There was no maternal mortality in the entire series.

The over-all fetal mortality in the series of 592 breech presentations was 4 per cent. No fetal deaths occurred in the cesarean section group. Fetal death rate in spontaneous breech delivery was 2.7 per cent in the primigravidas and 2.6 per cent in the multiparas. The death rate in the extraction series was 5 per cent in the primigravidas and 7.3 per cent in the multiparas.

This markedly increased fetal death rate in the group delivered by extraction (double among the primigravidas and triple among the multiparas) is a potent argument against routine breech extraction. If a well-trained and experienced group of specialists cannot avoid such a marked increase in fetal death rate accompanying breech extraction, how can we justify a recommendation for routine breech extraction?

DR. SEELEY (Closing).—Dr. Rucker asked why we had so many more breech cases in the first group. The reason is that they represented deliveries from two hospitals and in the last group most of the cases were taken from the hospital in which we do our private work and the skill of the attendants was greater. That is why the discrepancy shows up in the way it does.

DR. PAUL TITUS, Pittsburgh, Pa.—Dr. Seeley's splendid summation of the subject of breech presentation is difficult to discuss adequately because it touches on so many different points of importance. *Fetal mortality* is the criterion which he has used in judging what is safe and what is dangerous in this complication.

His paper clarifies many points, and leaves others still somewhat unsettled, probably purposely so. For example, he establishes, contrary to a common impression, that pelvic contraction is not a probable etiological factor in breech presentations; that the etiology of this condition is more likely to be fetal than maternal, and that prematurity is one of the chief fetal factors.

He finds from his extensive analysis that frank breech does not increase fetal risk, nor does early rupture of the membranes, except for prolapsed cord. He finds no added risk in attempts at external version if properly done, but in all that has to do with breech presentation he emphasizes, quite properly, that the skill of the attendant is of the greatest importance in accomplishing a minimal death rate. All of this is helpful to an important degree.

Nevertheless, he leaves us undecided on the still debated question of whether extraction should or should not be done promptly after the patient enters second stage. I should like to add only three points to Seeley's comprehensive study and analysis of this subject.

The first of these is approval of extraction of breech presentations promptly after they have entered the second stage of labor. The second is that forceps be used on the aftercoming head except in those, such as prematures, that can be delivered almost spontaneously. The third is that especial gentleness in resuscitation be observed. Sudden compression of the aftercoming head to pass the pelvis brim is probably much more traumatizing and shocking than the gradual moulding of a vertex presentation, so that resuscitation methods must not add to this.

DR. G. D. ROYSTON, St. Louis, Mo.—Dr. Seeley is to be congratulated on his low fetal mortality in breech delivery. There are a few points in this connection that I want to emphasize.

The arcuate uterus may be considered as one of the possible etiological factors and especially so where recurrences are common after external version. Three Kotex pads snugly strapped with adhesive to each side of the abdomen, to narrow the transverse uterine diameter until moderate engagement occurs, usually within one to two weeks, or labor begins, will usually prevent recurrence of breech presentation after external version.

Dr. Seeley's excellent results were obtained by these deliveries being conducted by highly trained experts. The majority of such cases are now, and for an indefinite future will be, delivered by those of less obstetric training, skill, and judgment. Some three years after completing my residency, I delivered three breech presentations in one month, with an infant mortality of 100 per cent. Since that time, I have had a very wholesome fear of this condition. For the past 34 years I have followed the method of Bumm, which is as follows:

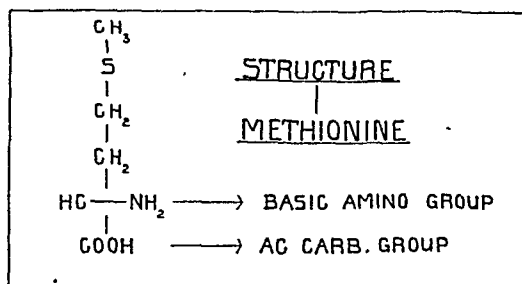
- a. Do nothing until the posterior buttock is visible at the vulva. At this point the breech and usually one or both thighs alongside have passed through the cervix;
- b. Place the patient's hips well over the edge of the delivery table;
- c. Give 1 c.c. of pituitary extract intramuscularly;
- d. Under light obstetric anesthesia, make a mediolateral episiotomy incision. The great majority of infants will then be quickly and spontaneously born. A small number requiring assistance in delivering the aftercoming head can be easily delivered with the Piper forceps.

Bumm emphasized that all expulsive force should come from above, which uniformly maintains flexion of the head and lessens the frequency of extension of the arms. These latter points greatly determine fetal dangers during delivery, according to Potter.

DR. LOUIS E. PHANEUF, Boston, Mass.—Because of my interest in the subject presented by Dr. Seeley, I had the breech deliveries at the Carney Hospital reviewed for a period of ten years, from July, 1937, to July, 1947. The Service is a combined one, having 62 beds, 33 gynecologic and 29 obstetric. There were 7,200 deliveries with 240 breech extrac-

intake for an adult.³ It is an essential amino acid being provided only from foods and cannot be synthesized in the body. It is chiefly obtained from serum albumin, egg-white and milk.

Amino acids are indispensable for the formation of proteins. In addition, all have specialized individual functions. For example, methionine donates both active methyl and sulfydryl groups. Cystine was once considered to be the essential sulphur-containing amino acid but this place has now been given to methionine. In this case, however, the dispensability of cystine is only relative; if cystine is not provided in the diet, enough methionine must be given to furnish the combined requirements of methionine and cystine to meet the metabolic needs. Methionine also serves as a source of active methyl groups. The quantity required for this purpose will depend upon the availability of other methyl donators such as choline which should also be present in the diet.^{6, 7, 8, 9, 10}



In animal experimentation, methionine is shown to be lipotropic, having a favorable influence on the liver similar to the combined action of cystine and choline. Administration of this substance prevents fatty infiltration of the liver. In spite of low protein intake, liver protection is afforded if methionine is given.³ Miller and Whipple were able to demonstrate the same beneficial effects if methionine were administered to protein-deficient dogs just before or after deep chloroform anesthesia.²

We agree that results of experiments in animals do not always coincide with clinical results found in the human being. Nevertheless, treatment of certain complications in obstetrics merits study relative to liver and kidney damage. There is definite clinical evidence that *acute* degenerative changes are beneficially affected by this substance and, though there have been clinical reports to the contrary, the chronic lesions may also be benefited by its use.^{11, 12, 13, 14}

Beams and Endicott have recently published their work relative to cirrhosis of the liver in the human being. Severe cases responded well to diet high in methionine content. Results were further improved by a methionine supplement. This clinical improvement was substantiated by liver needle biopsies and histologic examination of the tissues. The study suggests that methionine was responsible for the improved histologic changes in the liver.

Four obstetric complications readily lend themselves to such a study. These are the toxemias of pregnancy, infectious hepatitis occurring in pregnancy, postdelivery shock associated with the hepatorenal syndrome, and hemolytic disease of the newborn. Our observations and results will be divided into four parts.

THE USE OF METHIONINE IN OBSTETRICS*

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(From the Royal Victoria Hospital, McGill University)

THE liver and the kidneys are vital organs in every human being. Of necessity, they must play an even greater role in pregnancy. Consequently when certain complications occur, the essential functions of these organs are frequently found to be impaired.

Experimental hepatic and renal damage in animals has been produced by various methods. Necrotizing nephrosis in combination with hepatic injury has been caused by purely dietary restrictions; these manifestations were similar to those found in the human being where the hepatorenal syndrome occurred.¹ Administration of chloroform, phosphorus, or other chemicals also caused marked liver necrosis. However, these added chemical factors were contingent on the fact that dietary deficiency played the predisposing role in the causation of this damage.²

Gyorgy notes the similarity of experimental nutritional necrosis in the kidneys and liver to the pathologic findings in the eclamptic patient. Hypoproteinism is a most frequent finding in both conditions. This protein depletion may be the common factor which renders the liver more susceptible to damage by hepatotoxic agents.

Glycogen has been established for many years as a liver and kidney protective. But only recently has protein been proved to play a most important role in the protection of all body tissues. Normal liver and kidney functions can be maintained only when there is adequate protein intake.³ On account of these facts, the diet in pregnancy should fulfil certain requirements. It must be acceptable to the patient and it should allay hunger. A well-balanced diet is essential relative to protein, carbohydrate, and fat intake. There should be adequate vitamin and mineral content. Sufficient protein should be supplied to replace wear and tear of tissue in the mother and, at the same time, supply the needs of a growing fetus. This does not always take place.

It has been shown that if acute protein depletion does occur restoration of proper levels may be obtained by the intravenous administration of normal or concentrated plasma, protein hydrolysates, or the use of various amino acids.⁴

Our attention has recently centered upon the possible value of methionine as an adjunct in the treatment of certain obstetric complications which have frequently ended fatally. We know that methionine is a very necessary part of the normal diet; workers have estimated that 2 to 5 Gm. is the normal daily

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

All patients included in this table were admissions to our toxemia service. Those who demonstrated normal blood values for pregnancy showed no evidence of edema. This symptom appeared with lowered plasma-protein levels and edema became marked when the total protein blood level fell below 4 Gm. Both albumin and globulin fractions dropped in those toxic cases included in this series; the ratio showed only slight variation and thus could not be considered significant. (Table II.)

Liver function undoubtedly plays a major role in the case of the toxemic patient. Estimation of impairment is difficult. Numerous liver function tests have been employed but they are all found wanting in some respect. We are now trying a battery of flocculation tests; for our use the most reliable is probably the cephalin-cholesterol flocculation test. This aims at determining liver deficiency. Though the findings are variable, this test shows in Table III that the liver is frequently affected by true toxemia of pregnancy. It also demonstrates that impairment is more pronounced in those cases which are more severe from a clinical aspect.

TABLE III

CEPH. CHOLESTEROL FLOCC. TEST IN PREGNANCY.				
JAN. 1947 - MARCH 1948				
DIAGNOSIS	TOTAL CEPH. DONE	TOTAL CEPH. NEGATIVE	TOTAL CEPH. POSITIVE	% POSITIVE OF TOTAL
HYPERTENSION	6	5	1	16%
PRE-ECLAMPSIA	20	13	7	35%
ECLAMPSIA	5	3	2	40%
RENAL DISEASE	2	1	1	50%
TOTAL TOXIC CASES	33	22	11	33.3%
NORMALS	31	29	2	6.45%

During the last four years, we have had the same routine orders for toxemia patients in the Royal Victoria Hospital. These orders include complete bed rest, adequate balance of fluid intake and output, and proper bowel management. The diet has been neutral ash and low in salt; protein intake is 110 Gm., plus carbohydrate 275 Gm., and fat 90 Gm. Induction of labor has been initiated when indicated.

Recently, we have supplemented our routine treatment with quantities of whole blood or plasma in selected cases.¹⁸ We have also attempted to evaluate certain protein preparations by mouth and by the intravenous method. Methionine has been used in the severe types of pre-eclampsia and in all eclamptic patients. When possible, this is given by mouth in 0.5 Gm. tablets or crystals dissolved in tomato juice; 5 to 10 Gm. is the usual daily dose. When it is given intravenously, we have used as much as 20 Gm., diluted to a 2 to 3 per cent solution in 5 per cent glucose and water.

There have been seventeen severely toxic patients who received methionine for periods from one to four weeks. They include eight pre-eclamptics, six eclamptics, and three severe cardio-renal cases with superimposed toxemia of pregnancy.

Twelve of these cases were treated in the Royal Victoria Hospital, while five others were under the supervision of J. L. Macarthur in the Montreal General or Catherine Booth Hospitals. Every individual was severely toxic. In

Toxemia of Pregnancy

There is a tendency to hypoproteinism during pregnancy. Toxemia causes this condition to become more pronounced. Macarthur has shown that hypoproteinemia coincides with increased plasma volume; the resulting protein and hematocrit levels expressed in percentage are practically identical throughout pregnancy. He found that there was a difference of thirty per cent in pre-eclampsia, while in eclampsia the variation was even more striking, with a rise in hematocrit levels and a marked fall in plasma proteins.¹⁵

It should be emphasized that plasma proteins do not fall until after protein reserves are used from such organs as the liver, kidneys, and alimentary tract.¹⁶ Recent work also shows depletion of muscle and fascia before the blood levels fall.¹⁷ As a direct result of this depletion, the vascular, liver, and kidney functions are impaired. The effects of this impairment act as indicators in assessing severity of disease and prognosis; for example, one considers extent of edema, quantity and quality of urinary excretion, presence of jaundice, or other manifestations of liver impairment.

TABLE I

<u>TOXEMIA CASES: 1944 - 47</u>			
	<u>NO.</u>	<u>MAT. MORT.</u>	<u>FETAL MORT.</u>
PRE-ECLAMPSIA	361	1 (.3%)	44 (12%)
ECLAMPSIA	22	3 (13%)	8 (36%)
NEPHRITIC TYPE	15	0	6 (40%)
ESS. HYPERTENSION	38	0	2 (5%)
<u>TOTAL</u>	436	4 (.9%)	60 (13%)

TABLE II

<u>RELATIONSHIP OF OEDEMA TO PLASMA PROTEIN IN</u>				
<u>PREGNANCY. SEPT. 1946 - JAN. 1948.</u>				
<u>GRADE</u>	<u>TOT. PROTEIN</u>	<u>ALBUMEN</u>	<u>GLOBULIN</u>	<u>A/G RATIO</u>
NO OEDEMA - 14 CASES	6.31			
MILD OEDEMA - 27 CASES	5.77	3.60	2.01	1.79
MOD. OEDEMA - 24 CASES	5.56	3.47	1.91	1.81
SEVERE OEDEMA - 4 CASES	3.73	2.25	1.30	1.73

In our clinic, toxemia of pregnancy occurs frequently. At present, there are more deaths which are attributed to this cause than to any other complication in obstetrics.

Edema is commonly caused by a depletion of plasma proteins as shown by Table II.¹⁶

TABLE V

ECLAMPSIA

	No.	Type	Convulsions		Parity	A.P. Care	Delivery	Fetus	Clinical Liver Tests	Maternal Results
			Before	After						
<u>Routine</u> + <u>Methionine</u>	a	AP at 6 mths.	7	0	iii	MD? Out of town	Bag Induction	Dead-born	Ceph-Floc, neg. Oedema +++	a Good AP diuresis.
	b	AP at 9 mths.	3	2	i	Treated in Clinic for toxæmia	R.M.I. After 5 th convulsion	3020 gms. Alive + Well	Ceph-Floc - Tr; Itchy skin. Epigastric pain. Oedema +++	e Poor diuresis BL R; ^{150/90} until D.P.P.V.
	c	AP at 8 mths	2	0	i	None	R.M.I.	1600 gms.	Ceph-Floc +++ Oliguria - marked Oedema ++	All other cases
	d	Intra-Partum	3	0	i	Good M.D.	Mid-Forceps	3500 gms. Alive + Well	Ceph-Floc. +++ Oedema +	Rapid diuresis
	e	R-Partum 4 hrs.	4	0	ii	Good Staff	Twins	2200 gms. 2000 gms. Alive + Well	Ceph-Floc. Not Done Oedema +++	Rapid fall in BL R,
<u>Routine</u> <u>Treatment</u>	f	AP at 6 mths	6	1	ii	MD in Malone?	Bag Induction	Lived 2 days	No Liver Function Tests Done	Good diuresis
	g	AP at 8 mths	12	0	i	None	Spont.	Dead-Born Morphine Narcosis?		3 Mths Follow Up
	h	Intra-Partum	1	0	i	Poor Clinic	Low Forceps	3210 gms. Alive + Well		BL R; normal Urine Neg.

TABLE VI

CARDIO-VASCULAR RENAL DISEASE WITH PREGNANCY-METHIONINE R.									
ONSET	PAST HISTORY	PRESENT	PREG.	DELIVERY	FETAL R.	MATERNAL RESULT.			
a 24 WKS	SCARLET FEVER	BL/PR.	195/105	SPONT AFTER 10 DAYS R _x	PREVIABLE	BL/PR 150/90			
	WITH NEPHRITIS	ALB	++++			GOOD DIURESIS			
	T-ECLAMPSIA	CASTS	++			3 RD DAY - METHIONINE R _x			
	T-SEVERE PRE-ECLAMP	OEDEMA	+						
b INITIAL CLINIC VISIT AT 26 WKS	T-PREMATURE-DETH	BL/PR.	220/120	CAES. SECTION AT 32 WKS	1100 GMS. A and W	POST-OPERATIVE : GES.			
	T-BIRTH INJURY	ALB.	++++			SHOCK PLASMA BLOOD HYPERTONIC FLUIDS → BL/PR. RECOVERY			
	III-1938 - A and W	FUNDAL	: GES.			OLIGURIA + JAUNDICE			
	Oct. 44 - HYPERTENSIVE	OEDEMA	+			DIED - 48 HOURS			
g ?	G-Vs. DISEASES	BL/PR.	240/120	UNATTENDED HOME DELIVERY	A and W				
		ALB.	++++						
		OEDEMA	++++						
	PARA. XII	POST-PARTUM ADIM				POST-PARTUM : GES.			
	HEADACHES - 2 YRS	OEDEMA	++++			SHOCK PLASMA BLOOD HYPERTONIC FLUIDS → BL/PR RECOVERY RT. HEART FAILURE			
	DYSPOEA - 2 YRS	CEPH. FLOCC.	++++			OLIGURIA + JAUNDICE — METHIONINE R _x RECOVERY.			
		LIVER AT UMB. O							

addition, there was some added indication for its use such as definite evidence of hypoproteinism, edema, or oliguria as shown in Tables IV, V, VI.

TABLE IV -

PRE-ECLAMPSIA SEPT. '46 - MAR. '48

ROUTINE WITH METHIONINE.	NO.	ONSET	PARITY	PREVIOUS HISTORY AND PRESENT PREG	A.P. CARE	DELIVERY	FOETUS	CLINICAL FEATURES	MAT RESULT IN HOSPITAL	FOLLOW-UP.
ROUTINE WITH METHIONINE.	4	a AT 57 WKS	III	1944 NEUROSIS LABILE BL/PR	CLINIC	R.M.I.	2460 gms	XS GAIN IN WT BL/PR ¹⁰⁰ / ₁₃₀	EXCELLENT DIURESIS	6 MTH BL/PR ¹⁴⁰ / ₁₇₀ URINE - TR.
		b TWINS AT 57 WKS	I	PROTEIN DEFICIENT DIET	CLINIC	R.M.I. PROLONGED LABOUR	2385 gms 3200 gms	XS GAIN IN WT BL/PR ¹⁵⁶ / ₁₁₀ ALB +++ CEPH.FLOC neg	EXCELLENT DIURESIS (ON DISCH.)	5 MTH. NO CX BL/PR ⁹⁸ / ₆₀ URINE NEG.
		c AT 38 WKS	I	ASTHMA ARRESTED TBC.	CLINIC	MEDICAL INDUCTION	3105 gms	6016 WT GAIN BL/PR ¹⁵⁰ / ₉₀ ALB ++ CEPH.FLOC neg	GOOD OUTPUT BL/PR ¹⁵⁰ / ₈₅	—
		d AT 28 WKS	I	NEGATIVE	CLINIC	R.M.I + BAQ AT 32 WKS	1660 gms	12 LB WT GAIN 4 MTHS ALB ++ BP ¹⁴⁵ / ₉₀ GOOD OUTPUT CEPH FLOC neg	A.P. DIURESIS BL/PR ¹³⁰ / ₈₅	—
ROUTINE.	20	36-40 WKS - 10	I - 10	RECURRENT TOX.	CLINIC - 12	SPONT - 10	WT 2500 gms	AWGAIN 27 lb	GOOD - 16	11 CASES
		32-36 WKS - 6	II - 3	TWIN PREG.	OUT of TOWN - 5	R.M.I - 8	AWGAIN 14	RESIDUAL	} 4	NORESIDUAL - 10 HYPERTENSION - 1
		28-32 WKS - 3	III - 2	FOETAL ABNS.	2 CASES	SECT - 1	LESS 2500 gms	HYPERTENSION		
		2 nd TRIMESTER - 1 (MOLE)	IV - 1 V - 2 VI - 2	MOLE	1	CARD DECOMB HYSTERECTOMY (MOLE)	AWGAIN 4 DEAD BORN - 1 (TRAUMA)	MILD TOX - 13 MOD TOX - 4 SEVERE 3		

Diuresis was the most promising feature following this special treatment.¹⁵ It occurred in some instances a few hours after the first administration, especially when the methionine was given intravenously. In several instances, this diuresis occurred in the antepartum state when there was a failure with other forms of ordinary medication, including ammonium chloride and intravenous glucose solutions. There was also a coincident favorable response in the diminution of edema. With reference to the general correction of the protein deficiency further investigation is necessary.

The one patient who died was poorly treated. This was not entirely due to our neglect. It occurred when we had just commenced the use of methionine and there were other unfortunate circumstances. She had advanced cardiorenal disease and was six months pregnant when admitted to hospital with severe toxemia. Her condition improved considerably with routine treatment and the use of methionine. After three weeks of therapy she left hospital, signing a "refusal-of-treatment" form. Twelve days later she was readmitted in a critical condition. A cesarean section was performed which was immediately followed by coma, hemorrhagic diastasis, and jaundice. She was treated with repeated blood and plasma transfusions but death ensued forty-eight hours later. Autopsy examination revealed massive necrosis of the liver. We did not use methionine intravenously because, when this case occurred, our knowledge of its action and reaction was most limited.

Hepatorenal Syndrome

Active therapy is most necessary in any case of postdelivery shock. Many women who develop obstetric shock with persistent hypotension have been allowed to progress to jaundiced and anuric states without active measures being initiated.

Shock should be treated with plasma.¹⁸ Blood loss must be replaced by whole blood, and methionine should be given intravenously in a glucose solution to aid the plasma in preventing edema, anuria, and the consequent kidney and liver damage. Four cases have been treated in such a manner during the last eighteen months. Whole blood and plasma were given in adequate amounts and this was supplemented with 10 Gm. of methionine given intravenously in 500 c.c. of glucose and water. If indicated, this was repeated in 12 hours; one woman received 30 Gm. in 24 hours with no apparent ill-effects. Repeat doses were given by mouth for several days.

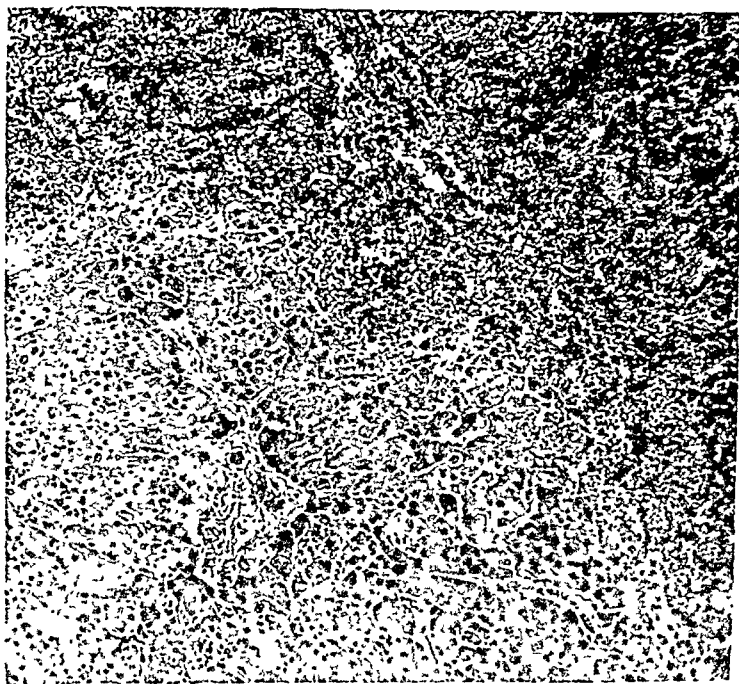


Fig. 2.—Liver in toxemia of pregnancy. Sections of the liver show large, irregularly arranged areas of hemorrhagic necrosis in which the parenchymal elements give evidence of various stages of destruction from simple necrosis to disintegration with extensive hemorrhagic extravasation. This section of liver damage is very similar to those published by Gyorgy, where experimental hepatic necrosis was caused by protein deficient diets.

All cases treated had the typical picture of the so-called hepatorenal syndrome; persistent systolic pressure under 100 with occurrence of anuria and jaundice. The complicating factors in these cases were:

- (1) Abortion with hemorrhage and anesthetic shock.
- (2) Elderly primipara with three-day labor and postdelivery shock
- (3) Placenta previa with massive hemorrhage and subsequent disruption of wound.
- (4) Severe cardiorenal disease with postpartum hemorrhage.

These four cases all fall into the group which previously would sometimes progress to cortical necrosis of the kidney or acute yellow atrophy of the liver. Every case survived under the described management.

All other cases indicated a beneficial result with the use of methionine. However, it is realized that this toxic series is far too small a number from which to make conclusions.

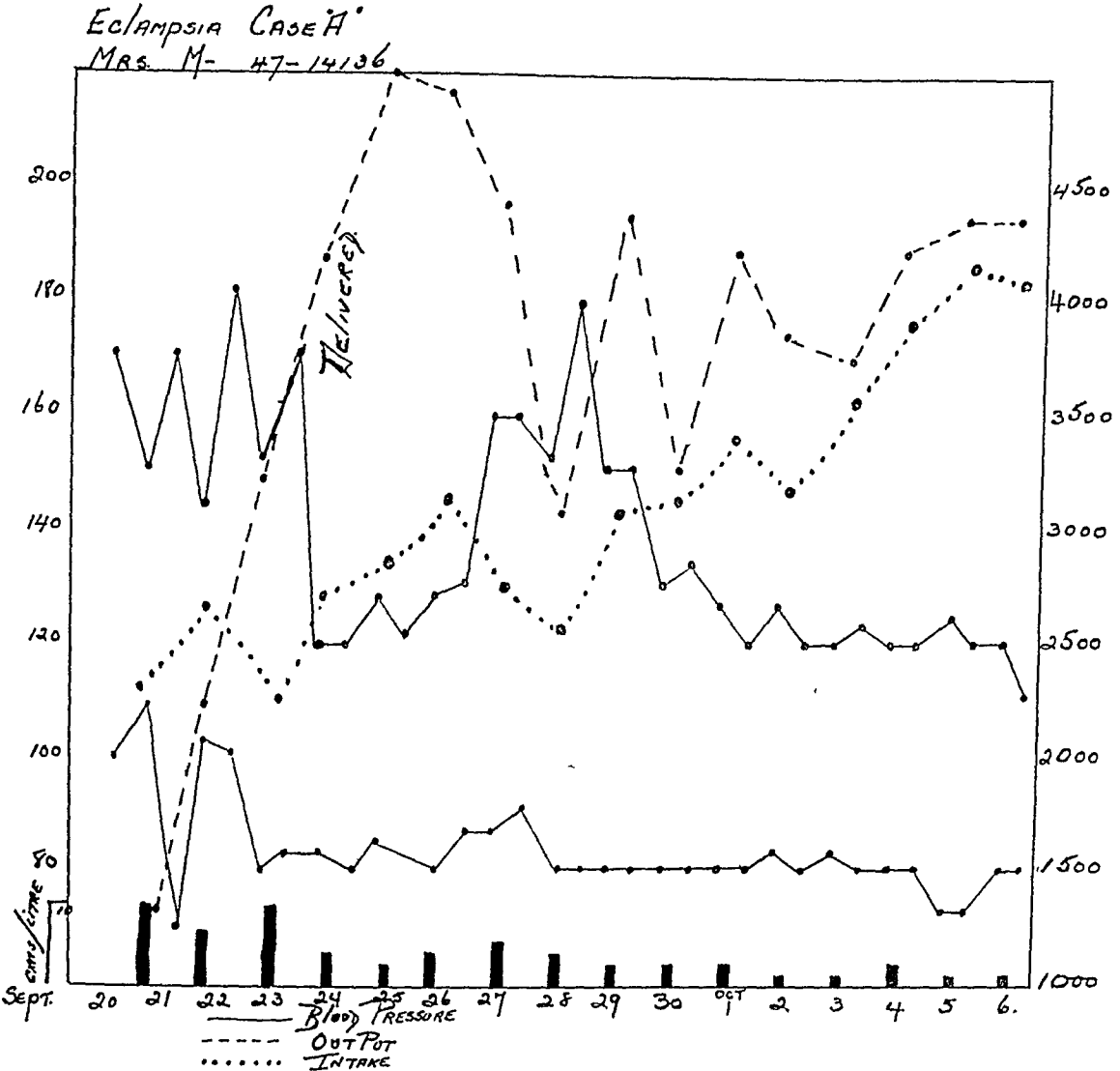


Fig. 1.—Eclampsia, methionine. This patient had recurring convulsions for two weeks in a small hospital. Diet was low in salt but also low in proteins. On admission she was in a comatose state and showed marked edema with oliguria. Daily intravenous methionine was given, 20 Gm. in 2,000 c.c. glucose and water. Note the urine output was far in excess of fluid intake preceding and during labor. Edema was practically absent at time of delivery. Albuminuria was 10 Gm. per litre the day after admission.

Infectious Hepatitis in Pregnancy

This condition has been found to be more serious in pregnancy due to the fact that acute liver damage is more prone to occur and residual cirrhosis is more frequent than in the nonpregnant individual. We have had three cases where methionine was used. Ten Gm. were given each day in conjunction with 5 Gm. of choline for the express purpose of liver protection referable to prevention of necrosis or cirrhosis. In no instance was the course of the disease shortened, but all three patients progressed favorably with no apparent residual damage.¹² One case was seven months pregnant when the jaundice appeared. She delivered seven weeks later with no toxic manifestations nor any increase in blood loss at the time of delivery. The other two cases occurred in the first trimester of pregnancy and both individuals are awaiting delivery.

on routine ante-natal examination. This was considered to be greater than the normal maximum daily requirement of the pregnant woman. Such a dose would provide a therapeutic systemic concentration sufficient to deal with moderate liver damage. No attempt was made to assess the woman's daily consumption of methionine in her foodstuffs and any she so obtained was regarded as a supplement.

POST PARTUM PROGRESS	CLINICAL	12 HRS	24 HRS	48 HRS	72 HRS	8 th DAY	
	COMA	SLIGHT	SEVERE	±	0		0
	JAUNDICE	0	+++	++	+		SLIGHT
	DYSPNOEA	+	++	+	SLIGHT		0
	LABORATORY						
	HGB.	68	74	76	77		75
	PROTHROM.	36"	34"	27"	23"		16"
	TOTAL PROT.		4.8	5.1			5.6
	CO ₂	30	36	47	39		48
	N.R.N	39	51	46	40		38
	CREAT.		4.4	3.3	2.6		1.2
HEPATO- -RENAL SYNDROME	BILIRUBIN DIRECT		4.	2.7	1.7		.6
	INDIRECT		5.9	4.	2.4		.8
	CEPH. FLOCC.		+++	++++	++		+
	THYMOL T		0	0	0		0
	THYMOL FLOCC		0	0	0		0
	P.C. SUGAR		90				72
	ALK. PHOS		15.2				
	KETOSTEROIDS						1770
	URINE ALB.	2 GRS	4.	2.	.5		0

Fig. 3B.—Clinical and laboratory findings, in the case of hepatorenal syndrome, as shown also in Fig. 3, A.

It was assumed that in the normal course of fetal development, as the need for methionine was manifested in the fetus, then the positive balance available in the maternal organism would be drawn across the placenta by the fetus. This is in accord with the generally accepted and proved theory of fetal demand and maternal supply. Since methionine is an essential amino acid, its passage across the placenta would be uninhibited.

When receiving methionine, the mothers were seen every two weeks before the birth of their babies. A constant check was made on their consumption of the drug and on the antibody blood levels. No case of idiosyncrasy or untoward reaction to the drug was noticed and no patient had to discontinue taking the drug because of nausea. The only complaint was of the tediousness of having to take ten fairly large tablets day after day. In some cases, treatment was for more than 150 days, a total of approximately 1,000 Gm.

The clinical material and controls were selected by discussing the problem of the unborn baby's chances of survival with the mother when her blood first showed antibodies. Most of the mothers in the severer groups could easily appreciate the facts. Excepting three patients who had been severely immunized by recent blood transfusion, all others had experience of previous fetal catastrophes, such as erythroblastotic babies, or babies born dead as a result of the disease. In the milder stages, Groups 1 and 2 (Primrose, van Dorsser, and

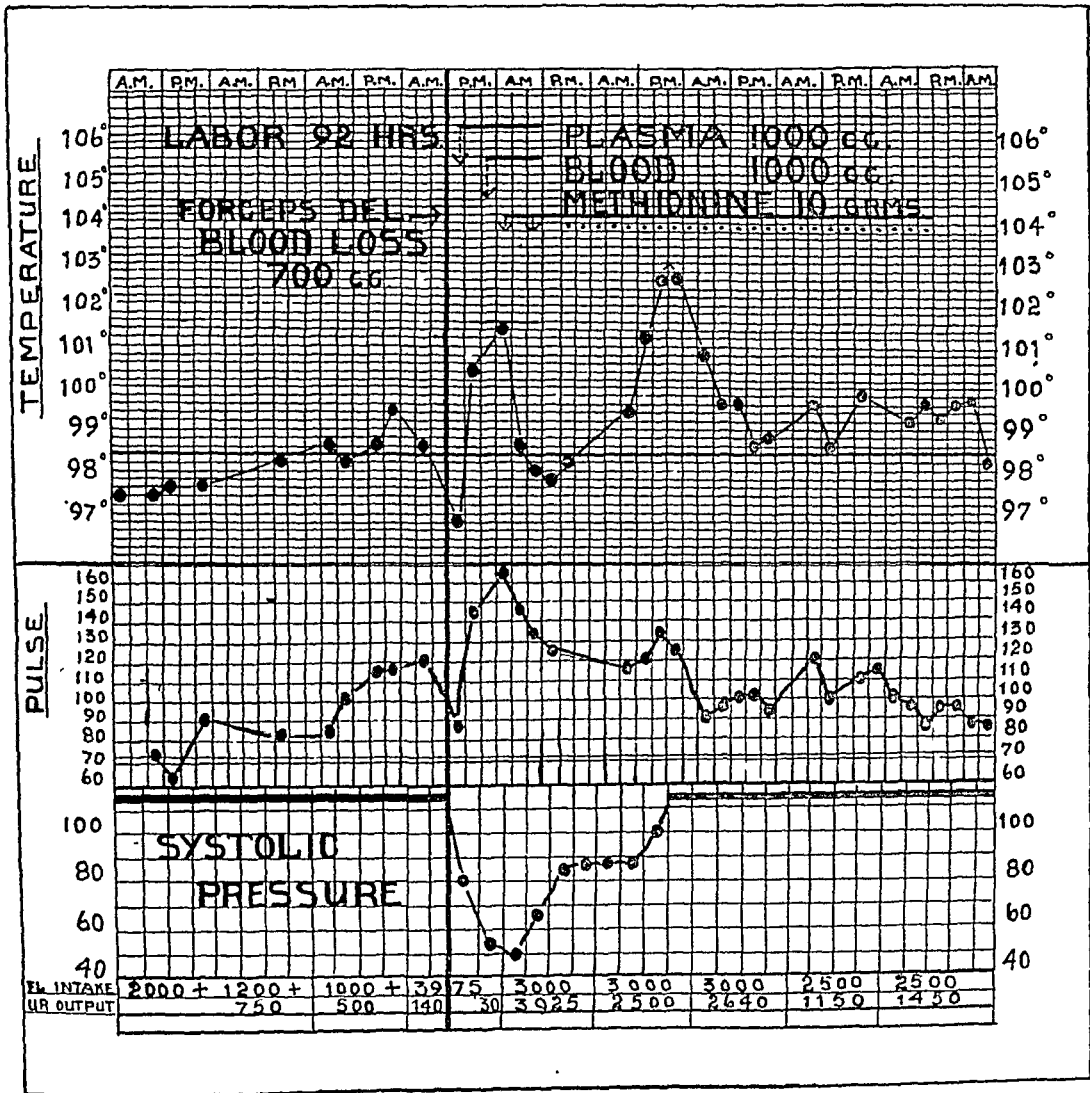


Fig. 34.—Hepato renal syndrome. This patient had 92 hour labor and difficult forceps delivery. Antepartum dehydration was accentuated by 700 c.c. blood loss post partum. Shock occurred two hours later with the subsequent hepatorenal syndrome. Note the elevated temperature, increased pulse rate, and marked depression of blood pressure. Anuria was present for eight hours. Urine output was observed by means of retention catheter for five days post partum.

Methionine in the Treatment of Erythroblastosis

When the pathologic processes involved in hemolytic disease of the newborn were studied from the clinical and postmortem material, it was obvious that fetal damage to the liver in varying degrees was present in every case.¹⁹ This damage, when once sustained, was thought to be very long lasting, as shown by the follow-up on our own cases and by the work of R. J. Drummond and A. C. Watkins in England.²⁰ They showed that the liver damage in young persons who were thought to be suffering from idiopathic congenital cirrhosis of the liver was in fact due to the late effects of erythroblastosis due to Rh incompatibility. Taking these facts into consideration, it seemed reasonable to attempt the protection of such fetal livers by the use of methionine whose action as a liver protector had been the subject of so much recent investigational work.²¹

Judging from the available data on daily requirements, an arbitrary dosage of 5 Gm. daily of the crystalline methionine was given, in tablet form to each mother as soon as the first signs of immunization to the Rh-factor was detected

marked and can readily be seen without the statistical analysis. In these three groups, nineteen control cases had one survivor equalling 5.25 per cent survival. Of twelve cases receiving methionine, ten babies were born alive, and eight survived, giving a gross survival rate of 66.6 per cent.

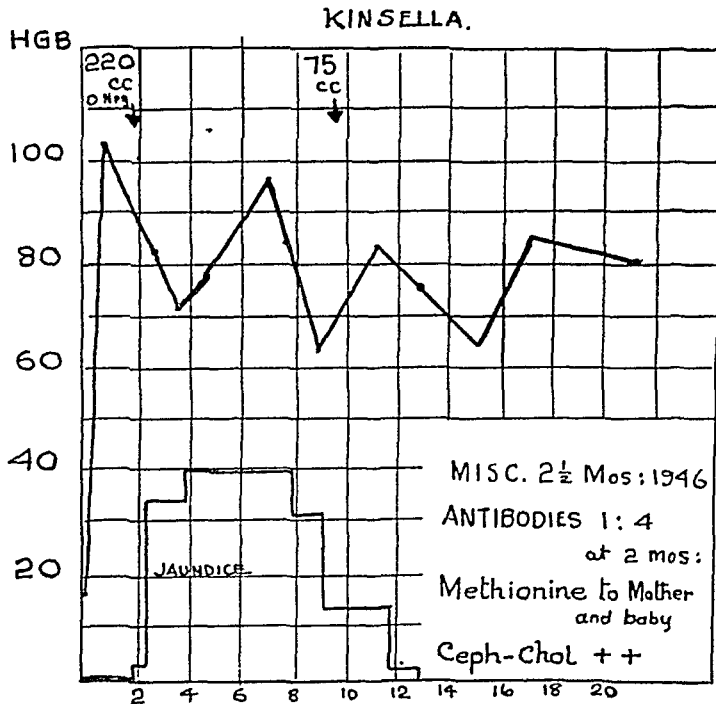


Fig. 4.—Methionine for hemolytic disease of newborn. Mother had 2 previous pregnancies; the first was normal, the second ended in miscarriage. Antibodies were present throughout present pregnancy and showed a 1:64 dilution at 37 weeks. Rupture-of-membranes induction was followed by low-forceps delivery. Mother received over 1,000 Gm. of methionine during four months of pregnancy. Baby received 0.5 Gm. daily for twenty-one days. Blood at birth showed 18 per cent hemoglobin and 1,300,000 red blood cells. Only two transfusions were given, the first being Rh-negative Group O, 220 c.c. whole blood.

In Group 4, the methionine cases labeled as deadborn happened to be twins, which died in utero three days before term. It is interesting to speculate what might have happened if these babies had been induced prematurely or had a cesarean section two weeks before term. The other two babies were born alive and transfused in our usual manner. Both apparently did well for the first three days but one died on the fourth day of atelectasis, and the other died on the sixth day of pulmonary hemorrhage.

In Group 5, the survivor in the control group was Rh negative, but died before leaving hospital of multiple congenital defects. In the methionine group, the deadborn case happened in a woman who had had three previous erythroblastotic babies, all deadborn. She came to us for antenatal care, being four and one-half months pregnant. At this time she showed a fairly high antibody titration. She was immediately placed on methionine, but the damage had been done. She aborted three weeks later of a deadborn macerated fetus.

It should be emphasized that in this disease we are using methionine purely as a liver protective. We know that antibody development occurs as usual in the mother and hemolysis of the red blood cells occurs in the fetus. Our point is that we can treat severe anemia in the newborn but we cannot adequately treat a severely damaged liver.²² One baby in this series had a hemoglobin of 18 per cent and a correspondingly low red-cell count but responded well to transfusion treatment because the liver was not severely damaged; the cephalin-cholesterol test showed only minor impairment.

Philpott²¹), the use of methionine was not pushed as we were confident that the babies would do well without treatment. However, quite arbitrarily, one case was selected in Group 1 and three in Group 2 and the others used as controls.

When it was obvious that any case was going to fall into the more serious Groups 3, 4, or 5, a most intensive effort was made to talk the mothers into taking methionine with the assurance that we hoped by this means to obtain for them a live baby. All clinic cases were offered the chance but in each group a certain proportion could not be so persuaded; these cases, together with a few private patients whose doctors chose to carry on with observation of their titrations but without methionine, formed a convenient source of controls. The only other medication given these patients was a ferrous sulfate preparation of iron and a multiple vitamin capsule, both in routine use in our clinic.

All erythroblastotic babies born during the year 1947 and up to May 1, 1948, are included in this experiment and are reported.

Samples of cord blood from the liveborn group were examined and the presence of hemolytic disease of the newborn, by our criteria, was confirmed. The deadborn group were subjected to careful pathologic examination and the nature of their disease was studied.

Further cord blood was examined by a battery of liver function tests as a routine. The pediatricians in charge of the cases recorded their clinical findings at birth. Each baby was examined by at least two pediatricians, and at no time before examination did they know whether a baby was a methionine case or a control. Of the liver studies available, only the cephalin-cholesterol flocculation was consistently affected in the severe cases.

Within the limits of the quantity of material available, 45 cases, the original premise is considered vindicated as shown in Table VII.

TABLE VII. HEMOLYTIC DISEASE OF THE NEWBORN

CONTROL CASES AND THOSE IN WHICH METHIONINE WAS ADMINISTERED TO MOTHER AND BABY						
GRADE	CASES	DEAD BORN	ALIVE BORN	SURVIVED	STATE OF LIVER	CEPHALIN-CHOLESTEROL
1.						
Control	10	nil	10	10	Slight to mod. liver enlargement	+++
Meth.*	1	nil	1	1	No liver enlargement	neg.
2.						
Control	3	nil	3	3	Palpable liver and spleen	++++
Meth.	3	nil	3	3	No liver or spleen palpable	+
3.						
Control	3	2	1	1	Liver and spleen enlarged	+++
Meth.	4	nil	4	4	Liver and spleen just palpable	+ to ++
4.						
Control	4	4	nil	nil	Advanced erythroblastosis	?
Meth.	3	1	2	nil	Slight liver and spleen enlargement	++
5.						
Control	9	8	1	nil	Hydrops, etc., aborted	?
Meth.	5	1	4	4	Liver and spleen just palpable	++

*Meth.—Methionine cases.

The cases have been divided into grades, and the methionine group in each grade has been compared with the control group. The results are apparent, and the difference between the control group and that having methionine is well seen throughout. Grades 1 and 2 are only mentioned in passing, because no claim is made for any significant difference in the survival rate, although both the clinical and biochemical studies show a significant difference between the two groups. It is in the severer grades, 3, 4, 5, that the difference is most

We have heard unofficially of occasional embolic reactions supposedly from these precipitated crystals. It has not happened in our institution. One case of the hepatorenal syndrome showed a severe reaction to the massive use of plasma plus methionine, from which one learns a great deal. She had been anuric and was markedly edematous. By administering large doses of plasma plus methionine too much fluid was withdrawn from the edematous tissues before an outlet was obtained by increase of urinary excretion. Right-sided heart failure and pulmonary edema were the result. This condition was relieved by the use of ouabain and the fact that diuresis occurred soon after, the patient excreting 2,430 c.c. in twelve hours.

Conclusions

1. Studies in the use of methionine have been carried out in four obstetric complications.
2. The results have been most promising but not conclusive. In the treatment of toxemia and hemolytic disease of the newborn, it is a valuable adjunct to other proved types of therapy.
3. The hepatorenal syndrome can be best treated with the combined use of plasma, whole blood, and methionine.
4. This investigative problem merits further study.

We wish to thank Dr. J. L. Macarthur for contributing the five toxic cases in this series. Thanks are also extended to Dr. J. S. L. Browne and Dr. Martin Hoffman for their cooperation relative to liver function tests.

The methionine used was kindly supplied by John Weyth & Brother (Canada).

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Discussion

DR. L. M. RANDALL, Rochester, Minnesota.—Modern physiologic concepts indicate that a liver containing adequate stores of glycogen, protein, vitamins, and normal amounts of fat,

All babies who have hemolytic disease receive 0.5 Gm. of methionine daily for at least the first twelve days of life. This is given in doses of .125 Gm. in 5 per cent glucose saline or in the milk. Practically all the babies have taken this mixture with avidity, almost denoting that they required it in their systems.

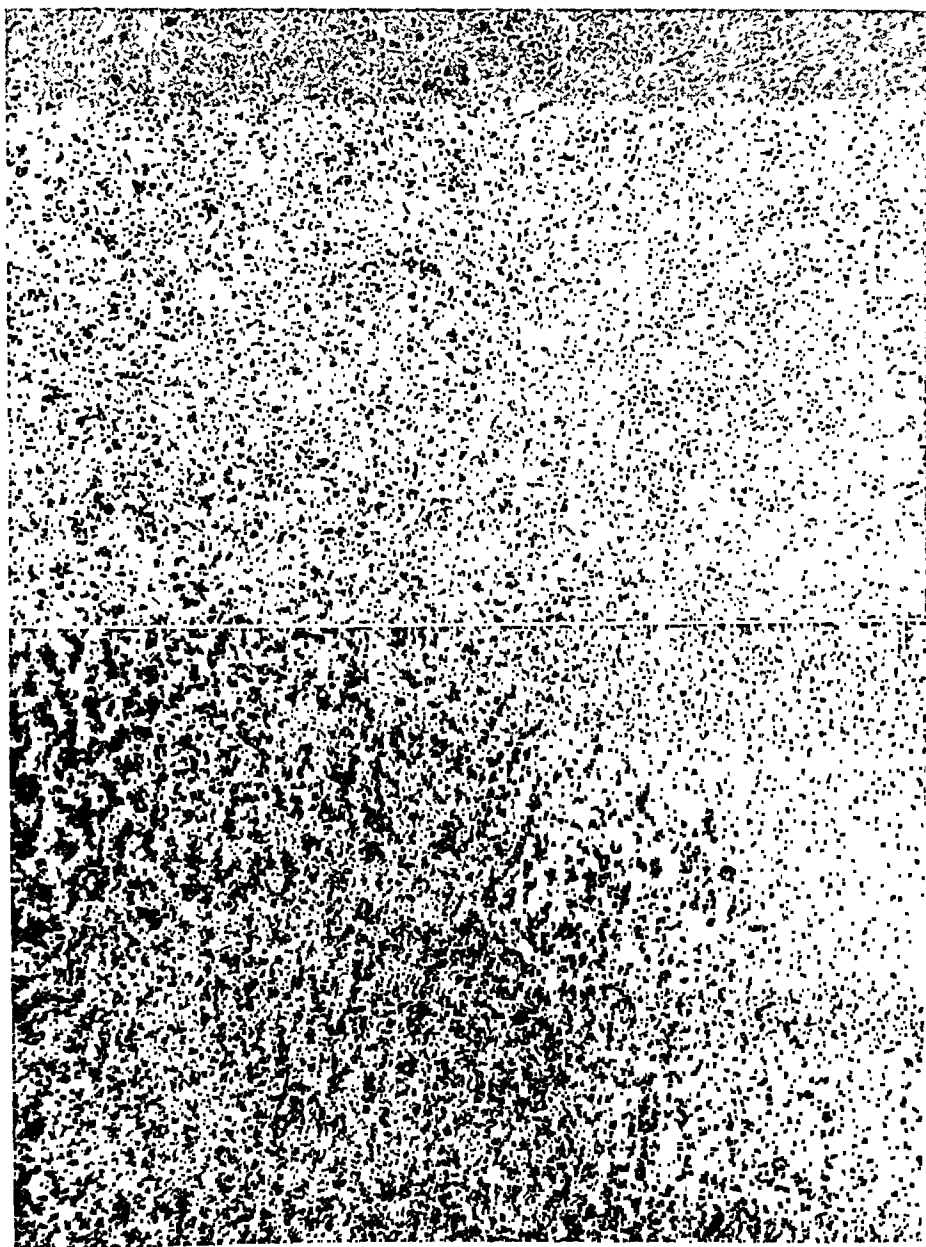


Fig. 5.—Comparison between liver sections from autopsies in erythroblastotic babies where the mothers had high antibody titrations during pregnancy.

Reactions to Methionine

In prescribing any new substance one should be inquisitive with reference to possible reactions. In this instance it is especially true, due to the fact that some protein hydrosalysates given intravenously have produced adverse reactions. Many cases have complained about the size of the pill and some about the taste. We have found tomato juice the best vehicle when methionine is given by mouth. In intravenous use, the crystals tend to precipitate if left standing any length of time or if the solution is more concentrated than 3 per cent. Our procedure is to mix and autoclave 10 Gm. in 200 c.c. of distilled water; this is then added to 300 c.c. of 5 per cent glucose solution.

in the reticular structure and cirrhosis. When cirrhosis associated with fat deposition in the liver occurs, it has been demonstrated in human subjects, by taking repeated living biopsy specimens, by measuring the liver function by the thyroid turbidity, cholesterol flocculation, serum alkaline phosphatase, change in the albumin-globulin ratio, and serum bilirubin, that treatment with lipotrophic substances lessens the fatty deposits in the liver and produces clinical improvement and improvement in the liver function as measured by these functional tests. However, this is thought to be the only value of methionine and these lipotrophic substances as far as liver damage is concerned. They have been tried in other forms of toxic hepatitis and experimental toxic hepatitis in anemias and have been found to be of little or no value.

There are several points in Dr. Philpott's paper which need further elucidation. Does he agree with Gyorgy that the lesions in the liver in eclampsia are the same as those found in nutritional necrosis? My feeling from autopsy material which I have studied inclines me to the view held by the older writers that the lesion is primarily periportal and associated with portal thrombosis and, further, that an important group of cases show no demonstrable changes in the liver as measured by the gross or microscopic picture.

It is also necessary to explain why it is that patients on an adequate protein diet still develop this toxemia and that the disease almost disappeared toward the end of the first World War in Germany and Austria when the women were on a very limited protein diet.

In the last twenty-seven years, we have treated our pre-eclampsics and eclampsics on a markedly restricted protein diet with the result that convulsive eclampsia and death from this disease has almost disappeared. Our patients are put at bed rest and given 1,000 c.c. of milk and this is continued until it is evident that the toxemia is controlled or that this regime will not control the toxic symptoms. Only a small percentage fail to respond, if not of the fulminating variety. Our series now consists of nearly 1,400 cases.

Dr. Philpott has properly pointed out the unsatisfactory status of liver function tests, and this, when combined with the rather small number of severe eclamptogenic toxemia cases reported here (17), makes him hesitate to draw sweeping conclusions.

It would seem from the reports in the literature that methionine has been of no value in acute infectious hepatitis and the results in the three cases here reported are inconclusive.

The value of this agent in combating shock seen in the hepatorenal syndrome can only be determined by its use in a large number of cases and by its use in alternate cases. I may say that in these cases I am especially careful to avoid the use of whole blood, especially when the patient may be of the pre-eclamptic group. I have seen fatal anuria develop days after the shock was controlled, even when the blood was carefully cross-matched and typed. Of course, in the presence of severe postpartum hemorrhage as in the case cited by Dr. Philpott, one has no choice but to use blood. The use of methionine in erythroblastosis as a prophylactic measure to protect the liver and permit the fetus to combat the anemia and jaundice of the first few days of life is logical if continued use shows that it will produce the results here reported.

It should be distinctly understood that this paper is in the nature of a preliminary report. Observations are carefully made of the use of a new substance in the treatment of several of the severe complications of pregnancy. This is the only way that information of a reliable nature can be acquired. We are indebted to Dr. Philpott for blazing the trail in this connection.

DR. PHILIP F. WILLIAMS, Philadelphia, Pa.—From a previous review of this subject, I was interested to find out how much methionine could be obtained by a moderately high protein diet. From several sources, Block and Bolling's, and Sahyan's books on amino acids and a number of journals of chemistry and nutrition, I have filled in, as far as possible, the calorie, protein, and methionine content of a diet quoted in Sahyan's book.

Sahyan suggests an intake of 1.9 Gm. as minimal and an intake of 3.8 Gm. as optimal to protect a 70 kg. man. In chick growth studies, these intakes are apparently synonymous

and which can maintain these stores, manifests the greatest resistance to toxins. These concepts also indicate that after hepatic disease is established an increased intake of carbohydrates and protein is necessary to maintain the stores in the liver and promote regeneration. Thus, the fundamental principle of prevention and treatment of liver disease is to supply these substances in an adequate diet, or by tube feeding or parenteral administration when necessary. The essayist has emphasized the value of an adequate, well-balanced diet in pregnancy. I believe, in general, the average recommended diet is too low in protein and that more protection would occur if greater amounts of protein were included in the diet during pregnancy.

The value of methionine, one of the essential proteins in the treatment of liver disease, has been subject to considerable controversy. Equally reliable authors disagree. The work of Beams and Endicott, in cases of chronic liver disease, based in part on microscopic studies of liver tissue, must be considered significant. The known functions of the liver are many and interrelated. The seriousness of liver disease seems to depend upon the impairment of metabolic activities. One of the difficulties in the interpretation of the results of therapeutic trials in liver disease in general is the suitable criteria for comparison. In individual cases, there often appears to be a variable relationship between clinical and biochemical findings. The results of the tests, as reported by the essayist, are examples.

The flocculation tests, such as the cephalin-cholesterol, depend on alteration of plasma proteins. The essayist presents estimations of the amounts of plasma protein in thirty-five patients experiencing edema and shows no great reduction except in four cases with marked edema but he does not give other components of their examination. Flocculation tests were performed on 25 patients, experiencing either pre-eclampsia or eclampsia, of which 35 per cent were positive. I would like to inquire whether he has demonstrated a correlation between the results of these two tests?

The information concerning the use of methionine in infectious or serum hepatitis, an example of a relatively acute condition, is at considerable variance. The recovery rate is sufficiently high to preclude definite conclusions as regards such specific treatment.

The treatment of shock is primarily one of prevention and, if it occurs, the immediate administration of parenteral fluids. Cannon's definition of shock will fit any condition regardless of cause and, aside from supplying red cells if hemorrhage is concerned, the need is to restore volume of circulating fluid and not for any specific protein, as methionine. Naturally, if a patient is allowed to remain in shock, certain reactions can occur and such specific treatment may be of value.

The employment of methionine in the prenatal period, where evidence of Rh sensitivity exists, deals with 28 patients and within the limits of such a small series the results are encouraging but, as the essayist states, will need further study.

This paper is a preliminary conservative statement from a man with an inquiring mind who enters a very complicated field. He should be commended and encouraged. I may close with a statement made by Dr. F. C. Mann, whose investigations of the behavior of the liver are well recognized, "The known functions of the liver are but part of the physiologic processes involving other organs and tissues of the body."

DR. F. H. FALLS, Chicago, Ill.—The function of the liver is of paramount importance in the physiology of the pregnant woman. The increased metabolic activity seen during pregnancy, the need to meet extra nutritional demands imposed by the developing fetus, and the activity of the placenta throwing into the maternal blood end products of protein metabolism which demand detoxification before their excretion by the kidney, all impose an additional burden upon the liver. When present in abnormally great amounts, these toxins act deleteriously on the liver cells and produce a toxic hepatitis which is reflected by decrease in the liver function as measured by certain tests and by histologic changes seen in the liver of women dead of these toxemias.

Methionine, choline, and cystine are lipotropic substances and have been found to be useful in the treatment of dietary and cirrhotic fatty degenerative changes in the liver. Normally, an adequate supply of methionine, choline, and other lipotropic substances permits of a utilization of the fat and prevents its deposition in the liver cells leading to changes

In a minor degree, fat is also a "protein sparer." It does not naturally follow that just because the Europeans had little meat in their diet, there was little protein; vegetable protein has not as high a biologic value as animal protein but it is still protein.

In toxic cases it is most difficult to arrange a satisfying diet which contains more than 100 Gm. of protein. The patient feels "stuffed" after such a meal. We use egg-nogs which are fortified with protein, and these are given between meals. It has been suggested that this protein intake is not necessary for the normal individual. I do not think that we should consider a pre-eclamptic patient normal, especially if she is losing 10 Gm. of albumin in the urine each day. It should be replaced.

As I have previously stated, this is a preliminary report and we are experimenting with a problem which has proved to be most fascinating.

with the terms essential and replaceable. Macarthur has recently quoted Gyorgy to the effect that the prevention of hepatic injury in human beings may be accomplished by an intake of from 2 to 4 Gm. of methionine, or a protein-rich diet with a high methionine content, and mentions that the fat in such a diet should be limited. The methionine content of the diet shown is approximately 33 per cent above the optimal daily intake of methionine for men. For a 56 kg. woman, such a diet should have a high protective value.

It would necessitate the ingestion of ten quarts of milk to obtain 10 Gm. of methionine. In order to obtain an additional 6 Gm. of methionine, a diet would have to be increased by at least two pounds of meat and three quarts of milk daily. The ingestion of such large amounts of food would seem to be out of the question for the average individual. I noted also in my research on the question of methionine content of the edible portion of various foods that chicken muscle ranked next after whole egg, while muscle meats, beef, pork, and lamb, were slightly lower and almost equal; the gland proteins, liver, kidneys, and sweetbreads have a lower content. Rice and shellfish muscle equal lean beef in value.

It is probable that chronic hypoproteinemias in pregnant women cannot be overcome when symptoms of toxemia arise, but if, from the very onset of pregnancy, an effort is made to have pregnant women ingest 100 Gm. of protein daily they will certainly receive an optimal protective intake of methionine. The cystine (dispensable amino acid) content of the diet should always be borne in mind, in regard to the total sulfur-containing amino-acid requirement, because of its sparing action on methionine.

DR. PHILPOTT (Closing).—The chief purpose of this essay is to provoke more interest in liver and kidney function relative to those obstetric complications previously mentioned.

Dr. Randall has asked if there is any correlation between the results of the cephalin-flocculation tests and the progress of the patients. This was certainly true in those babies with hemolytic disease. The babies who died or who had clinical evidence of severe damage all showed four plus cephalin-flocculation tests. In pre-eclampsia and eclampsia, the tests were certainly of value to demonstrate liver damage in the majority of cases, but there were a few who were clinically ill but who showed only plus one cephalin-flocculation, which we consider within normal limits.

In addition, one chart noted that some apparently normal pregnancy cases showed positive cephalin-flocculation tests. But this inaccuracy is true of all liver function tests. For example, the toxic patient who died of marked liver necrosis had a cephalin-flocculation test of plus two. The immediate cause of death was hemorrhagic diastasis and yet the blood showed her prothrombin time to be normal. Some people take the prothrombin time as an index of liver function but it certainly was inaccurate in this case.

With reference to Dr. Falls' remark about comparative pathologic findings in animal experimentation and those of eclampsia, most certainly there is some similarity in the widespread necrosis. However, Gyorgy shows that in animal experimentation the necrosis is usually central and midzonal but the cirrhosis is mostly periportal, where one also finds damage most evident in the eclamptic patient.

Dr. Williams and Dr. Falls both were inquisitive relative to ideas of high-protein diet for the toxic patient. I was most interested in hearing Professor Simmonet of Paris in a lecture a few months ago at McGill University. He stated that the toxic patient should have almost no protein in the diet and that carbohydrate should be increased. He referred to the low incidence of toxemia during the war years in Europe and the low intake of animal protein during those years. But that is not the whole story. Those people had diets fairly high in vegetable protein and he neglected to mention the "protein sparing" effect of carbohydrate intake. If carbohydrate is given correctly, especially orange juice and sugar, about three hours after a meal, the protein is spared in its use for wear and tear and it is stored away for future use.

fied in the hospital laboratory by the laboratory technician. Every specimen opened in the operating room was excluded from this study for technical reasons of bacteriologic principle. Uteri from postpartum patients were removed for the assurance of sterilization in all but three instances, where hemorrhage indicated the procedure. Postpartum hysterectomy is not the routine procedure to accomplish sterilization at The Chicago Lying-in Hospital. Consequently, postpartum hysterectomy at arbitrarily chosen times should yield bacteriologic and histologic samplings not available satisfactorily heretofore. Since attempts at aspiration by needle puncture through the anterior cul-de-sac were unsatisfactory, and since cultures taken through the cervical canal in the late puerperium could be conclusive only if they were negative, the above procedure was indicated for scientific study as well as clinical management. The obstetric uteri, taken directly from the operating room to the hospital bacteriology laboratory, were cultured in all but two instances in the laboratory by one of the authors (K. E. H.) using both aerobic and anaerobic techniques, as well as by the technician of the hospital laboratory. Following culture, the uteri were sent to the laboratory of clinical pathology for histologic evaluation.

Three of the postpartum patients had hysterectomy to arrest severe hemorrhage. The remaining fifteen patients of the original eighteen puerperal group were seen by one of the senior staff members as well as medical consultants, who agreed upon the indications for sterilizations. Moreover, a senior staff member approved and was present at each of these operations, to obtain the specimen in as unaltered a condition as possible, and for assurance of welfare to the patient.

TABLE I. CORRELATION OF BACTERIAL CULTURES AND PATHOLOGY OF 100 NONOBSTETRIC UTERI

HISTOLOGIC CLASSIFICATION	TOTAL NO.	PER CENT POSITIVE CULTURES	BACTERIAL CULTURES			
			UTERINE INVASION		NO INVASION	
			POSITIVE CULTURES	NEGATIVE CULTURES	POSITIVE CULTURES	NEGATIVE CULTURES
Leiomyoma	45	24		4	11	30
Adenomyosis	6	33		2	2	2
Malignancy	5	20	1			4
Hyperplasia endometrium	1			1		
Other (see Table II)	43	28	3	7	9	24
Totals	100		4	14	22	60

TABLE II. CLINICAL DIAGNOSES AND BACTERIAL CULTURES OF HISTOLOGICALLY NORMAL UTERI*

CLINICAL DIAGNOSIS	TOTAL NO.	BACTERIAL CULTURES			
		UTERINE INVASION		NO INVASION	
		POSITIVE CULTURES	NEGATIVE CULTURES	POSITIVE CULTURES	NEGATIVE CULTURES
Menorrhagia	17		6		11
Prolapse	17	3	1	6	7
Ovarian cyst	4			1	3
Pelvic inflammatory disease	4			2	2
Dysmenorrhea	1				1
Totals	43*	3	7	9	24

*The same uteri classified as "other" in Table I.

Results

The findings deviated somewhat from the expected picture. It will be noted from Table I that, of the 100 nonobstetric uteri, positive cultures were obtained from 26. The uterine invasion refers to curettement, soundings, or radium application preceding the hysterectomy. Thirty-four strains of both aerobic

BACTERIOLOGY OF THE GYNECOLOGIC AND INVOLUTING PUERPERAL UTERUS*†

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ALTHOUGH it is established that bacteria are regularly present in the postpartum uterus, adequate bacteriologic study has not been made of the involuting uterus; nor have bacteriologic findings been correlated with the histologic picture except in puerperal infection. It has been assumed generally that the normal nonobstetric uterine cavity is bacteriafree. The paucity of information on the bacteriology and histology of the gynecologic and involuting puerperal uteri has stimulated this study. Histologic and bacteriologic findings of eighteen postpartum uteri removed at varying periods from three and one-half hours to 125 days following delivery have been studied. For comparison, 100 nonobstetric uteri were similarly studied.

Review

The earlier bacterial studies on the flora of the various portions of the female genital tract have been reviewed by Kuster.¹¹ Special credit prior to this contribution may be given to Döderlein,⁵ Menge and Krönig,¹² Hallé,⁷ Bergholm,¹ Natvig,¹³ Wegelius,¹⁹ and others. More recently particular emphasis was directed toward the pathogens responsible for the febrile postpartum courses by Schottmüller,¹⁴ Schwarz and Dieckmann,^{15, 16} Harris and Brown (J. H.),⁹ Brown (T. K.),^{2, 3} Colebrook,⁴ Steinhorn,¹⁷ Stone,¹⁸ and Douglas and Davis.⁶ Hite, Hesseltine, and Goldstein¹⁰ studied the bacterial flora of the normal and pathologic vagina and uterus of 248 patients. In this group, the bacterial flora, as evaluated by cultural means, of the vagina of normal prenatal patients was similar to that of patients with mycotic and nonspecific vaginitis, but not vaginal trichomonas. A variety of organisms was removed from the postpartum uterine cavity of normal patients, as well as from those complicated by endometritis. The frequency of isolation of bacteria did not differentiate the febrile from the normal postpartum patients and was similar to that of vaginal trichomoniasis. These observations stimulated further studies of the organisms removed from the uterine cavity after delivery.

Material

The nonobstetric uteri removed for various conditions which are explained in Tables I and II were opened in the bacteriology laboratory after sterilization of the surface by searing with a heated spatula. The myometrium was incised and the cavity opened with sterile instruments. Material for cultures was taken by a sharp sterile curette and inoculated into dextrose brain medium and on aerobic and anaerobic blood agar plates. Isolated bacteria were identi-

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†Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

system because of the small number of eighteen. This group is listed chronologically by day postpartum of the hysterectomy. Hysterectomy was done primarily for purpose of sterilization, but the opportunity was thus afforded for adequate bacteriologic and histologic study of the uterine cavity. The febrile course that followed in five patients occurred in all within the first 45 postpartum days, and four within 28 days.

TABLE V. RELATION OF THE BACTERIAL CULTURES TAKEN FROM THE UTERINE CAVITY TO PUERPERAL INVOLUTION

CASE	DAYS POSTPARTUM	BACTERIAL CULTURES	REMARKS
C. H.	3½ (hours)	*†	
E. H.	9	†	Febrile postoperative course
M. H.	11	Anaer. Streptococcus*	
L. S.	18	Anaer. Micrococcus Diphtheroids	
V. P.	21		
E. W.	22		Febrile postoperative course
E. B.	25	Anaer. Streptococcus and Bacteroides	Febrile postoperative course
J. D.	29		
J. F.	38		Febrile postoperative course
C. R.	42		
H. G.	45		
T. K.	45		Febrile postoperative course
H. V. D.	52		
P. P.	53		
M. S.	54		
D. D.	68		
S. H.	80	Anaer. Micrococcus	Retained placental tissue
T. McG.	125		

*Cultures taken by laboratory technician.

†Profuse bleeding at time of hysterectomy.

The detailed histologic studies of these eighteen patients will be presented subsequently.

The postpartum uteri include eighteen specimens removed at times varying from three and one-half hours to 125 days after the delivery of the infant. They are fairly well distributed throughout this period and provide excellent material for study of the changes associated with uterine involution. All eighteen patients had satisfactory postpartum courses, but five had febrile postoperative periods.

The negative cultures obtained from the uteri received three and one-half hours and nine days after delivery are in all likelihood correlated with hemorrhage, since results of other studies indicate the presence of bacteria in the uterine cavity in the immediate postpartum period.

The four specimens from which positive cultures were obtained are of particular interest.

Those removed at eleven and eighteen days are uteri in which the placental site is still composed of degenerating necrotic tissue in which leucocytes are present. The leucocytes are found in greater numbers in the one removed at eleven days but are present in both. This would appear to be a type of tissue in which bacterial growth might well be expected. It seems probable from the appearance of these specimens that the majority of uteri removed during the first two to three weeks after delivery will contain bacteria demonstrable on culture.

The third specimen in which bacteria were found was removed at twenty-five days. It, too, shows many leucocytes and large necrotic areas in the placental site. The endometrium away from the placental site is fairly well developed, but many leucocytes are present in the most superficial portions. In some areas, the appearance is that of granulation tissue; numerous capillary-like blood vessels and a dense infiltration of mononuclear and polymorphonuclear leucocytes are present.

and anaerobic bacteria, including aerobic and anaerobic staphylococci, non-hemolytic aerobic streptococci, anaerobic streptococci, aerobic diphtheroid rods, *Bacillus subtilis*, and the anaerobic *Bacterium melaninogenicum* and other *Bacteroides*, were isolated. Positive cultures were obtained from four of eighteen patients who had preceding uterine invasion and in 22 of 82 patients who had not had prior instrumentation. The most frequently identified organisms were diphtheroid rods—9, *staphylococcus aureus* and *albus*—7 each, *Bacillus subtilis*—6, non-hemolytic streptococci—3, anaerobic streptococci—2.

The histologic classification, although rather inclusive, gives conditions present.

TABLE III. RELATION OF THE INTRAUTERINE CULTURES OF 100 HYSTERECTOMIES TO CERVICAL AND ADNEXAL CONDITIONS

TISSUE EXAMINED	HISTOLOGIC CLASSIFICATION	TOTAL NO.	PER CENT POSITIVE CULTURES	BACTERIAL CULTURES			
				UTERINE INVASION		NO INVASION	
				POSITIVE CULTURES	NEGATIVE CULTURES	POSITIVE CULTURES	NEGATIVE CULTURES
Cervix.—	Normal	28	14	2	7	2	17
	Cervicitis	68	28	2	11	17	38
	Malignancy	1					1
	Not removed	3					3
Fallopian tube.—	Normal	73	21	1	15	14	43
	Chronic Salpingitis	10	20		1	2	7
	Not removed	17	35	3	2	3	9
Ovary.—	Normal	72	18	1	17	12	42
	Cysts	14	29			4	10
	Not removed	14	43	3	1	3	7

TABLE IV. BACTERIAL CULTURES AND PATHOLOGY OF 15 POSTMENOPAUSAL UTERI

CLINICAL STATE	TOTAL NO.	INVASION		NO INVASION	
		POSITIVE CULTURES	NEGATIVE CULTURES	POSITIVE CULTURES	NEGATIVE CULTURES
Malignancy	5	1*	3†		1
Fibroid	3			2	1
Prolapse	7	1		4	2

*Radium 35 days before.

†Radium 54, 57, and 80 days, respectively, before hysterectomy.

The histologically normal uteri are appraised by clinical diagnoses for conditions which indicated the hysterectomy. The frequency of positive uterine cultures in these respective conditions is given in Table II. It is interesting that all seventeen patients with menorrhagia had sterile cultures. Perhaps the bleeding may have been a mechanical or physiologic factor contributing to these results, as is suggested by the finding of Hare.⁸ However, investigation of this point has not been made. On the other hand, the number of positive cultures in prolapse might be anticipated. A further relation (Table III) of the condition of the cervix, Fallopian tube, and ovary as related to the endometrial culture from the uteri removed in association with these conditions is offered for completion of the study. There is no apparent significance except perhaps in the instance of cervicitis. Although the bacterial culture and pathologic conditions of the fifteen postmenopausal patients (Table IV) is without particular significance, the data are presented for record. There is not a sufficient number with malignancy of the uterine cavity to find whether the apparent relationship is important. The relationship of the bacterial cultures taken from the uterine cavity (Table V) to the puerperal uterine invasion can be evaluated in protocol

Conclusions

Bacteriologic study has been made of material taken directly from the cavities of 100 gynecologic patients and eighteen involuting puerperal uteri following hysterectomy. The bacteriologic findings have been correlated with the clinical and histologic data. Positive cultures were obtained from twenty-six of the gynecologic specimens, and, with the exception of cervicitis, there was no apparent relationship to pathologic conditions of the adnexa or cervix, nor was there correlation with the presence of leiomyomas, adenomyomas, or malignancy of the uterus. Seventeen uteri removed because of menorrhagia failed to yield positive cultures, while, in prolapse of the uterus, bacteria were isolated from nine of seventeen specimens.

The findings in the postmenopausal uterus were not different from those of the menacmic uteri.

Bacteria were isolated from four of eighteen involuting puerperal uteri removed 11, 18, 25, and 80 days post partum. The bacteriologic and histologic findings can be correlated. Two uteri removed early (three and one-half hours and nine days) were bacteriologically sterile, but hysterectomies were performed because of active bleeding, a factor which undoubtedly altered the findings.

The identity of the bacteria is given, and the significance of the results is discussed.

The authors are indebted to Dr. Edith L. Potter for the histopathologic descriptions, to Miss Mollie Yasutake and Mrs. Marie Graves for their technical assistance, and to Dr. E. C. Turner for his assistance in reviewing the records.

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Discussion

DR. HERBERT TRAUT, San Francisco, Calif.—Problems of bacterial invasion, especially those of the uterus, are difficult to handle precisely. They do not fall easily into categories because of technical difficulties. If one regards the uterus as an area susceptible to bacterial invasion and then studies the flora of pathogenic organisms as they may be demonstrated in the puerperal or nonpuerperal uterus, there will be revealed a variety of invading organisms which would at first glance seem to be quite impressive. To offset this

The fourth specimen to yield positive cultures was removed on the eightieth day. An explanation for the presence of bacteria is readily available in the presence of a mass of placental tissue still attached to the uterine wall. The villi are hyalinized and a large amount of calcium is present. Between the placenta and the myometrium there is a wide irregular zone of leucocytes. It seems probable that wherever placental tissue is retained complete healing is impossible and bacteria may persist.

Discussion

The ages of the obstetric patients varied from 19 to 39 years. Two were between the ages of 19 to 24, 7 between 25 and 29 inclusive, 7 between 30 and 35, inclusive, and one at 36, and one at 39 years. Three of the eighteen patients had hysterectomies because of hemorrhage. The other fifteen, however, had hysterectomies to put an end to the reproductive career for eight different conditions. Rheumatic heart disease determined the procedure in six patients. Other indications occurred in progressively declining numbers.

It is interesting that anaerobic bacteria were isolated in all four instances. On the other hand, bacterial cultures of the nonobstetric uteri varied considerably, irrespective of uterine invasion prior to the hysterectomy. The bacteria are compatible with spread of growth upward from the vagina. In the uninvaded uteri, cultures of staphylococci and streptococci composed a slight majority over the other organisms. *Bacillus subtilis* is considered to represent contamination. The other types of bacteria have been isolated frequently from postpartum uteri or from the vagina.

The concept that the nonpregnant and uninvaded normal uterine cavity is free from bacteria needs re-evaluation according to the above findings. The presence of these bacteria in the uterus is consistent with obstetric findings, and their source is logically from the vagina. From the previous findings, it is evident that bacteria may remain in the postpartum uterus for a varying period of time following delivery. The persistence of microorganisms in the uterine cavity may be related directly to its placental site, its extrusion, and especially to retained placental tissue.

The obstetric patient has ordinarily been considered noninfectious. Present and previous observations indicate that after delivery the uterine cavity is infected or a potentially infected zone not unlike a draining abscess or cavity. One might use the term "laudable lochia" in comparing the bacterial behavior of the postpartum uterus with what took place in the early days of surgery. Mechanisms influencing the presence of microorganisms in the postpartum uterus have not been determined by this study. One contention could be that certain bacteria have digestive or other action upon the placental site and necrotic tissue remaining in the postpartum uterus. Accordingly, the obstetric patient is only relatively "clean" bacteriologically, as the uterine cavity and lochia in all puerperal patients harbor bacteria actually or potentially pathogenic. Consequently, it would seem that the unknown factors of microbiologic process in relation to recovery and regeneration of the puerperal and the invaded gynecologic uterine cavity can be solved by diligent, thorough, and well-controlled investigations.

which usually do not produce a true septicemia. Leonard Colebrook has shown by "in vitro" experiments that strains of the anaerobic nonhemolytic streptococci isolated from the puerperal genital tract will not multiply, and frequently are not able to survive a period of incubation in fresh defibrinated human blood, clots, or sera. He attributed this finding to the low pathogenicity of the organisms and to the bactericidal powers of the blood. Interestingly enough, reduction of the pH and a diminution of the antitryptic powers of the blood or sera resulted in a luxuriant growth of the same organisms under similar conditions. Furthermore, Colebrook demonstrated such chemical changes in the lochia and felt that the observations were significant in the explanation of the development of puerperal infection. We have frequently found negative cultures from the uterus at the time of cesarean section when bleeding was excessive and infection known to exist. Consequently, I feel that the presence of blood in these uteri may have been responsible for some of the negative cultures obtained. The same explanation may be tenable in some of the instances of negative cultures obtained following "invasion" of the uteri in the bleeding cases.

In connection with the relatively large number of positive cultures obtained when cervicitis existed, I would like to ask Dr. Hesseltine if the endometrium obtained for cultures was located in the region of the internal os (isthmic portion) or higher up, since the source might have a definite bearing on the result obtained at culture.

My experience has indicated that cancer of the endometrium is frequently infected but that the infection depends on the stage of the disease and on the extent of the necrosis and exfoliation. I believe the negative cultures obtained here are quite consistent with our understanding of this disease. They were obtained for the most part many weeks following radium therapy when there might be no necrosis and, accordingly, no infection. I feel confident, however, that this would not be the case if the disease were more advanced.

With regard to the puerperal uterus, Dr. Hesseltine has presented data indicating that the endometrium is sterile after the twenty-fifth day, except when there is retained tissue. Obviously, to obtain more exact information regarding the time microorganisms disappear from the puerperal uterus, more specimens will have to be studied in the early puerperium, particularly between the seventh and thirtieth days.

About fifteen years ago I carried out a number of experiments utilizing different types of apparatus to introduce a tube through the puerperal cervix in order to obtain cultures from the lochia in the interior of the uterus without contamination from the cervix. Considerable time and effort were spent in these studies and it appeared reasonably certain they were uncontaminated by the cervix. Uterine cultures taken by means of a modified Little tube at the same time gave almost identical results and accordingly for this reason and the complicity of the procedure, the method was abandoned. This, in my opinion, proved the value of cultures obtained in this fashion. The method employed by the essayist in correlating the bacteriologic and histologic findings, however, adds greatly to the knowledge acquired. The approach presented might well be utilized in an experimental study of the effects of sulfonamides, antibiotics or other chemotherapeutic agents.

DR. T. K. BROWN, St. Louis, Mo.—Dr. Hesseltine has discussed the bacteriology and histology of eighteen cases in which a postpartum uterus was removed at various times and for various reasons. Twenty per cent of these cases showed positive cultures; in each case the organism was found to be anaerobic in type. Five of these cases had febrile post-operative courses. Because of the wide distribution of these cases during the puerperium (three and one-half hours to one hundred twenty-five days) the histology portrays well the changes during involution. A description was given of the changes in the endometrium, the myometrium, and the vessels as involution progressed. In the control series of 100 gynecologic uteri, positive cultures were obtained in 25 per cent of the cases, irrespective of whether the uterus had been invaded or not. In the cases of prolapse of the uterus, there were positive cultures in 50 per cent. This would seem likely in this type of case, where the cervix is frequently protruding outside of the body and may be somewhat patulous and exposed to contamination.

first glance, we must be aware of the fact that the offending organism is possessed of widely differing degrees of pathogenicity, on the one hand, and that on the other there are subtle and little-understood mechanisms of resistance to pathogenic influences of bacterial origin. So, to speak of the presence of a bacterial agent capable under some circumstances of producing embarrassing clinical evidences is not final. We must eventually devise a scheme whereby we can more adequately evaluate the potentialities for harm that may be inherent in these invaders. We are all aware of the characteristics of the hemolytic type of streptococcus and have learned to beware and to institute drastic therapeutic remedies when its presence has been demonstrated. However, we know much less and need to learn more of the lower grade pathogenic microorganisms, which on occasion can assume potent influences for harm. It is with these factors that Dr. Hesseltine's paper has to deal. He has given us a factual account of a wide experience in nonpuerperal uteri and a lesser one in those following pregnancy. The story he has presented of bacterial invasion of the uterine cavity is impressive. One could wish that we could have as adequate a presentation of the various influences working in the bodies of his patients which made for serious or less significant pathologic damage.

It is necessary to make one point clear. We are on solid, familiar ground, so long as we are dealing only with the characteristics of well-known organisms. In the confusion involved in shifts of potent pathogenicity and ability of the individual to erect mechanisms of defense, we are still lost in quandary as to the full significance of our data. This presentation, though not as conclusive or as extensive as we need, fills in a chink in the mountain of accumulative data which will eventually be most helpful in solving our dilemma.

To be more specific: Dr. Hesseltine has given us evidence that the nonpuerperal uterus is more often invaded by somewhat pathogenic organisms than we had supposed. The chief incidence of this invasion occurred in patients who had an infected cervix or in those who had myomas or adenomyomas of the uterus. This is an important observation because it has a bearing upon therapeutic procedures. To curette or use radium under such circumstances must inevitably lead to a greater than normal incidence of inflammatory reactions and eventual damage. This may be regarded as the principal and most illuminating feature of his presentation.

The number of postpartum uteri studied may be considered to be too small for statistical evaluation. However, consider the difficulties attendant upon such a study. It can be only occasionally that such uteri may be obtained for the sort of scrutiny which he has given them. One might be critical and doubt the indications for the removal of some of the uteri which were included in this report. This would be small and undeserving, for neither you nor I were there to bear the clinical responsibilities for evaluating the situation. We must, therefore, in all professional charity repose confidence in our colleagues and accept this possible criticism as completely sub judice.

The important fact with respect to the puerperal uterus is that it is an infected organ and that, insofar as the data presented can show, it becomes relatively sterile after the twenty-fifth day post partum, excepting in those instances in which there are retained tissues not readily susceptible of exfoliation. In the latter case, the period of uterine return to a state of bacterial freedom may be indefinitely deferred.

In addition, Dr. Hesseltine has given us detailed and interesting data referable to the healing process of the placental site.

DR. GORDON DOUGLAS, New York City.—Dr. Hesseltine has approached and shed some new light on a problem which has long puzzled the gynecologist and obstetrician. The results of his thorough investigations would appear to justify the removal of many uteri, both in the puerperal and nonpuerperal states, when less radical procedures might have achieved the same clinical results. In this particular respect one is reminded of the material necessary for the last contribution of the late Dr. J. Whitridge Williams, which was presented before this Society at its meeting in 1931.

The most remarkable observation in the nonpuerperal uteri was the finding of sterile cultures from the endometrium of patients with bleeding. The organisms isolated are those

of streptococci being present in the pelvis and the patient not having sufficient resistance to withstand their invasion if operation were done early. This seems to be borne out in Dr. Hesseltine's series of eighteen cases in which five had febrile postoperative courses.

Dr. Hesseltine has mentioned the difficulty in the classification of bacteria found in his series. This is true because of the synergism of the organisms present. Frequently the aerobic and anaerobic bacteria are present at the same time. In the handling of such cultures, as one begins to obtain the pure culture from the original, there is a separation of the organisms and neither one of them grows out well as the isolation proceeds. The anaerobic bacteria grow poorer as the aerobic organisms are eliminated from the culture and, finally, about the time the organism is obtained in a pure state, it is suddenly lost. This is one of the reasons the classification of anaerobic bacteria has not gone further.

I should like to comment on the use of antiseptic vaginal instillations to combat the invasion organisms from the vaginal tract during labor, or subsequently, and also in gynecologic cases preoperatively.

I found that the use of 1 per cent neutral acriflavine in glycerine as an instillation the night before a gynecologic operation and also the morning of operation would sterilize the vagina and there would be less chance of bringing about the invasion of organisms into the uterine or abdominal cavity. Also, healing of the vaginal operative field was greatly enhanced. The vagina can be sterilized overnight by the use of such instillations. Instillation in obstetric cases is in large part responsible for the fact that we have had no deaths from puerperal infection since January, 1932, during which time we have had 32,640 deliveries up to May 1, 1948.

Several years ago, Dr. Carleton N. Price of Washington, D. C., and I made some cultures of postpartum patients in whom instillations had been used. The number and variety of organisms was greatly reduced as compared with cultures taken in cases in which instillations had not been used. Many cases never had any demonstrable growth from the uterus, post partum. Those that were positive cleared up in a much shorter time than one would expect.

In a paper on the "Bacteriology of the Uterus at Cesarean Section," which I presented before this Society in 1939, I concluded with the statement, "Antiseptic vaginal instillations offer a means of preparation of a patient for cesarean section which will: first, largely eliminate one of the most important causes of mortality, infection; second, reduce the incidence of positive uterine cultures obtained (to one-tenth of the incidence found where instillations were not used); third, make it relatively safe to postpone operation to a much later hour in labor; and fourth, lower the indications for the more radical operative procedures." Of course, intrapartum infection may occur and this can only be prevented by the earlier prophylactic use of the instillation.

DR. N. J. EASTMAN, Baltimore, Md.—In Dr. Hesseltine's present paper, as well as in other communications, he has stressed the fact that the postpartum uterine cavity is contaminated and has likened it to a draining abscess cavity. It will be the purpose of my remarks to call attention to the fact that the bacterial flora responsible for this septic state may be altered greatly by the intra-administration of penicillin. The method we have used was devised by Dr. Joseph A. Guilbeau, Jr., of my service. We employ a small tube 3 mm. in diameter over which a finger cot is stretched tightly and tied down at the proximal end. It is inserted and a pointed stylet is used to perforate the rubber over the end. The rubber then snaps back quickly.

Another stylet carrying a tiny piece of gauze is next introduced. This is rotated, withdrawn, and then cultured. All cultures from patients who had had penicillin were subject to treatment with chlorase so that any effect observed represents the effect of penicillin in vivo and not in vitro while being cultured.

All the bacterial work has been done by Mrs. Isabelle Schaub of our Department of Bacteriology. The cultures were taken between 36 and 72 hours after delivery. The results in untreated patients were in no wise different from those reported by other students of this subject and showed that anaerobic streptococci were present in the great majority of cases along with many other organisms. There were only two completely sterile cultures in the patients who had received no penicillin.

Cultures taken of the cervix, before the onset of labor, are usually negative except in cases with marked erosion. Before the expulsion of the mucous plug from the cervix, with the onset of labor, the patient's uterine cavity seems to be protected from organisms. However, as the cervix dilates, organisms may enter the uterine cavity irrespective of whether the membranes are present or not. In other words, the membranes do not offer very much obstruction to the invasion of bacteria and intrapartum infection can occur. I recall a case of a labor of approximately eight hours in which the membranes were not ruptured until the delivery of the baby was in progress; nevertheless, the mother had developed fever during this labor, the baby was stillborn, having died during labor. Cultures of the lung, blood, and peritoneal cavity of the fetus gave the same organisms which also caused the death of the mother three days later. The membranes, in this case, offered no protection from infection to either the baby or the mother.

Either during labor, or shortly thereafter, the uterine cavity becomes contaminated with organisms from the vaginal tract over a period of days and this finally is cleared up spontaneously as the lochial discharge diminishes. It is, therefore, important to eliminate all unnecessary trauma to the cervix or lower uterine segment and to limit manipulation as much as possible. One should do all that is possible to maintain adequate drainage. If this is accomplished, the patient will remain afebrile in spite of considerable contamination of the uterine cavity which is shown either by culture or by the odor of the lochia. In some cases, the mere presence of a tampon or sponge allowed to remain in the vaginal tract, will interfere with drainage sufficiently to cause this patient to have fever, and its removal is all that is necessary to allow the temperature to drop to normal. Perhaps a blood clot or a piece of membrane may act in a similar manner by obstructing free drainage from the cervical canal. I agree with Dr. Hesseltine that rather free bleeding from the uterine cavity, post partum, is conducive to a clean uterine cavity as the organisms are washed out. Of course, if hemorrhage goes to the point that anemia develops, then this makes it possible for a patient to become infected more readily, due to decreased resistance to the organisms.

In the study of bacteriology of uteri, postpartum or postabortal, I have divided the organisms found into aerobic and anaerobic organisms and also a mixed group in which both aerobic and anaerobic organisms were present. Aerobic organisms have been found alone in but 8 to 10 per cent of the cases; anaerobic organisms are encountered in from 45 to 50 per cent of such cases. In about 45 per cent of such cases, a mixed group of organisms are encountered, both aerobic and anaerobic in nature, and this is a group that is demonstrating synergism of organisms in these patients as referred to by Dr. Hesseltine in his series. As a rule, the anaerobic group of bacteria is predominant, being present in approximately 95 per cent of the cases, either alone or synergistically with aerobic organisms of various types. Necrotic tissue is suitable medium for the growth of anaerobic bacteria, as the tissue is detached from the normal circulation and its oxygen content is reduced to the point at which anaerobic bacteria can grow very satisfactorily. Such anaerobic organisms, especially the anaerobic streptococci are proteolytic in nature and digest this necrotic tissue causing it to eventually slough off. This proteolytic tendency may also bring about the invasion of thrombi and the eventual spread of the infection through the venous system, provided adequate drainage is not obtained and the uterine cavity cleaned of its debris. The spread, in this manner, brings about the development of thrombophlebitis. Finally, the dissemination of infection from the pelvis to the lung occurs, as is the case in which fatal infection develops.

In a case of postabortal or postpartum uterine infection, we are dealing with a wound infection and must treat it accordingly. I believe that most abortions are incomplete; at least microscopically, and usually some debris remains after the sac is passed. Some of the placental tissue frequently remains after delivery, although it may cause no demonstrable trouble. I have seen small portions of placental tissue retained for some months, causing considerable disturbance in the menstrual history and finally requiring removal before the patient is brought back to normal. In such cases, where placental tissue remains and is contaminated, involution of the uterus is usually delayed.

Dr. H. S. Crossen taught that gynecologic operations should be postponed for anywhere from four months to a year after a delivery or miscarriage because of the possibility

THE MORPHOLOGY OF THE HUMAN FALLOPIAN TUBE IN THE EARLY PUERPERIUM*

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SINCE 1941, women who have had eight or more viable infants have been offered tubal ligation at the Johns Hopkins Hospital. This indication is based on the finding of Eastman,¹ confirmed by Yerushalmy et al.,² that women of this parity face a threefold increase in maternal mortality over women in the lower parity brackets. Such a program greatly increased the number of sterilizations performed and would have been entirely impractical, because of limited bed facilities, had it not been for the feasibility of immediate and early puerperal sterilization.³ This procedure has been eminently successful, as will be shown in a forthcoming publication by Vosburgh and Rice which reviews the clinical aspects of this experience.

The present study deals solely with the morphologic findings in the Fallopian tubes from 715 of these sterilizations carried out between January, 1941, and June, 1947. This represents the material from the vast majority but not from all the tubal ligations, because, in a few instances, the pathologic specimens were either lost or were not fit for study. In no instance was the operation performed on febrile patients nor in any case in which the character of the labor or delivery suggested the likelihood that infection might ensue. All these 715 patients, in other words, were believed to be entirely free of any type of pelvic infection, actual or potential. Every effort was made, within the limitations of a busy obstetric service, to carry out sterilization as soon after birth of the infant as possible. The Pomeroy technique under Pentothal Sodium anesthesia was the method of choice for most of the operations. A small portion of the isthmus of both tubes was fixed immediately and submitted to the pathologic laboratory for examination. For the purpose of this study, all these tubes were reviewed and rediagnosed without regard to the previous diagnosis or to the clinical history. The data thus derived were placed on special punch cards and only then were the clinical data added. These cards were then sorted and the various correlations shown in the tables obtained. During the period under consideration, 46 interval sterilizations were performed as well as 35 ligations accompanying hysterotomy. These two series serve as controls where necessary.

Fig. 1 shows graphically the distribution of the cases according to time of operation. Zero days post partum is used to indicate ligation at the time of cesarean section. One day post partum then indicates operation within the first twenty-four hours, etc. All of the lesions described were divided according to degree into mild, moderate, and severe, but for the purpose of this paper these various categories are grouped together.

Acute Salpingitis.—This lesion varied from the mere presence of polymorphonuclear leucocytes in the lumen to marked swelling of the rugae with a dense infiltration of inflammatory cells, as seen in Fig. 2. Only in the most

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The results in the women who had received penicillin in labor were quite different. The amount given was 200,000 units at the onset of labor in the majority of cases. A minority also received 5,000 units after delivery up to the time the culture was taken. Recalling that in the 32 untreated cases we had only two sterile cultures, it is noteworthy that in this group of 54 who had received penicillin, 32 were absolutely sterile. Moreover, if we include as sterile those cultures showing the pleuropneumonia-like organism (which is known to exist normally in the birth canal and is regarded as nonpathogenic) the percentage goes up to 74. Three cultures show the colon bacillus which would not be expected to be affected by penicillin.

The six treated cases in which the anaerobic streptococci were demonstrated were ones in which the penicillin was given only in 200,000 unit doses, and had the penicillin been continued they also might have been sterile. Some plausibility is lent to this supposition in that nearly thirty-six strains of anaerobic streptococci were highly sensitive to penicillin by recognized tests of sensitivity to this organism.

It is not my purpose in making this report to suggest that penicillin be administered routinely in labor, but since these results conform with our clinical experience it seemed worth while to report them by way of saying that the great majority of organisms present in the puerperal uterus, including the anaerobic streptococci, are vulnerable to penicillin. The implications of this statement in regard to the treatment of antepartum and postpartum infections are obvious.

DR. HESSELTINE (Closing).—Pursuant to some of Dr. Traut's comments, we have been interested in the synergistic relations and results from the synergistic pattern and disturbance of the balance. The isolation of the anaerobes as well as the aerobes also follows along with some of Dr. Douglas' references. Our cultures were taken from comparatively high up in the uterine cavity, the incision being made in the corpus proper well up toward the fundus. This technique was developed originally since we did not know how long after delivery it would be necessary to continue the study. Cultures through the cervix have certain technical faults.

Dr. Eastman's reference to antibiotics is interesting. We have a report now ready for publication in which both penicillin and streptomycin were administered for prophylaxis. There was no reduction in the morbidity rate following penicillin therapy under the conditions of our study. On the other hand, the febrile puerperal course was reduced distinctly in those treated with streptomycin. Because of the dangers of streptomycin, this finding may be unfortunate, inasmuch as it may cause misuse or abuse of streptomycin with the development of drug-resistant strains and other hazards.

high percentage occurrence associated with the pregnant state, with a definite decrease after the third postpartum day. It is possible that the development of even a mild leucocytosis which sometimes occurs at term and is almost universally present in the puerperium could be responsible for this lesion. It is rare but not unknown in the nonpregnant state and appeared in 8.6 per cent of the 35 hysterotomies.

TABLE II. THE OCCURRENCE OF TUBAL LEUCOSTASIS IN 715 PUERPERAL STERILIZATIONS
DISTRIBUTED ACCORDING TO TIME OF OPERATION

DAYS POST PARTUM	STERILIZATIONS	LEUCOSTASIS ONE TUBE	LEUCOSTASIS TWO TUBES	PER CENT LEUCOSTASIS
0	165	17	24	24.8
1	178	15	23	21.3
2	158	12	5	10.8
3	90	6	6	13.3
4	48	1	1	4.2
5	24	0	0	0.0
6	11	0	0	0.0
7	13	1	0	7.7
8	4	0	0	0.0
9	5	0	0	0.0
10+	19	1	2	15.8
Control	46	2	0	4.3



Fig. 2.—Acute salpingitis.

Perivascular Round-Cell Infiltration.—The gathering of lymphocytes and plasma cells around the veins of the tubal muscularis is shown in Fig. 4. This cuffing of the veins occurs both in the pregnant and nonpregnant tubes with a fair degree of frequency. However, it would appear from Table III that this lesion is more prevalent during the pregnant state and the puerperium, espe-

severe forms was the muscularis invaded and this lesion has never appeared as advanced as in true, full-blown gonorrheal salpingitis. Bacteria could not be demonstrated by stain and there was no clinical correlation between this finding and the occurrence of puerperal fever. Table I shows the distribution of patients whose tubes showed acute salpingitis according to time of operation. It is obvious that the presence of an acute inflammatory reaction in the tubes is in direct correlation with the length of the delay from delivery to operation. While there seemed to be no relationship between this finding and the postoperative course of the patient, nevertheless, the presence of such abnormal tubes late in the puerperium would seem to be one additional factor in favor of early operation.

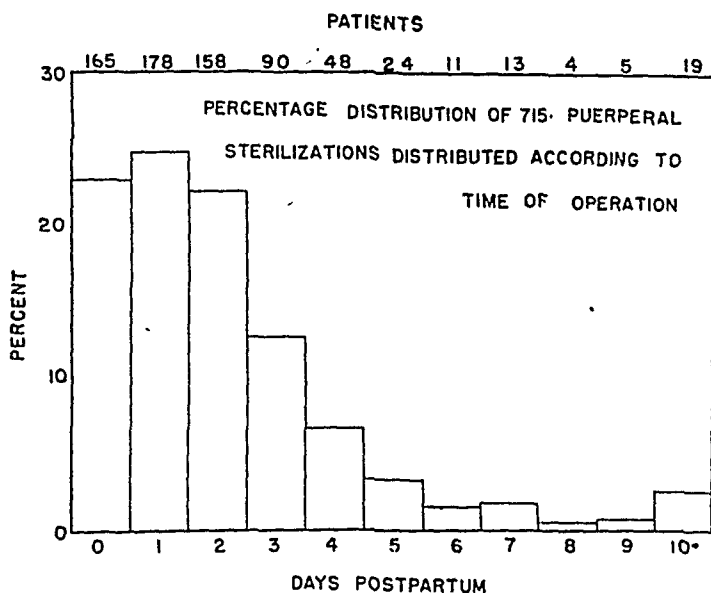


Fig. 1.

TABLE I. THE OCCURRENCE OF ACUTE SALPINGITIS IN 715 PUERPERAL STERILIZATIONS DISTRIBUTED ACCORDING TO TIME OF OPERATION

DAYS POST PARTUM	STERILIZATIONS	SALPINGITIS ONE TUBE	SALPINGITIS TWO TUBES	PER CENT SALPINGITIS
0	165	3	1	2.4
1	178	0	1	0.6
2	158	1	3	2.5
3	90	2	2	4.4
4	48	0	0	0.0
5	24	2	1	12.5
6	11	2	2	36.3
7	13	2	2	30.7
8	4	2	0	50.0
9	5	0	0	00.0
10+	19	2	2	21.0
Control	46	0	1	2.2

Leucostasis.—The pooling of leucocytes in veins associated with diseases where the presence of young white cells are common, such as leucemia, has been recently termed leucostasis. What this means is not clear but such pooling occurs in the presence of young white cells even though the count is not extraordinarily high and it has been suggested by Furth³ that the stickiness of the young cells in the relatively slow venous circulation may be responsible for this phenomenon. Such a picture is well demonstrated in Fig. 3. Table II shows a

cially from the third to the sixth puerperal days. This point of view is strengthened by the occurrence of perivascular round-cell infiltration in tubes of 35 per cent of the hysterotomies. This finding has no correlation with the presence or absence of syphilis in the mother, nor is it related to the occurrence of fever in the puerperium.

TABLE III. THE OCCURRENCE OF TUBAL PERIVASCULAR ROUND-CELL INFILTRATION IN 715 PUERPERAL STERILIZATIONS DISTRIBUTED ACCORDING TO TIME OF OPERATION

DAYS POST PARTUM	STERILIZATIONS	PERIVASCULAR ROUND CELLS ONE TUBE	PERIVASCULAR ROUND CELLS TWO TUBES	PER CENT PERIVASCULAR ROUND CELLS
0	165	14	17	18.8
1	178	6	9	8.4
2	158	6	12	11.4
3	90	9	13	24.4
4	48	6	8	29.2
5	24	0	5	20.8
6	11	2	0	18.1
7	13	0	1	7.7
8	4	0	0	0.0
9	5	0	2	40.0
10+	19	1	1	10.5
Control	46	1	4	10.8



Fig. 5.—Tubal edema.

Tubal Edema.—Fig. 5 is typical of this lesion. The rugae are swollen and the lymphatic spaces greatly distended with acidophilic material. This does not extend to the muscularis. Table IV shows this form of edema to be related to pregnancy and the early puerperium. It was not found in this series after the seventh postpartum day and did not occur in the control group.

Decidual Reaction.—The presence of tubal decidua in relation to ectopic pregnancy and endometriosis has been reported by numerous observers. Tilden and Windstedt⁴ have previously described its occurrence in association with

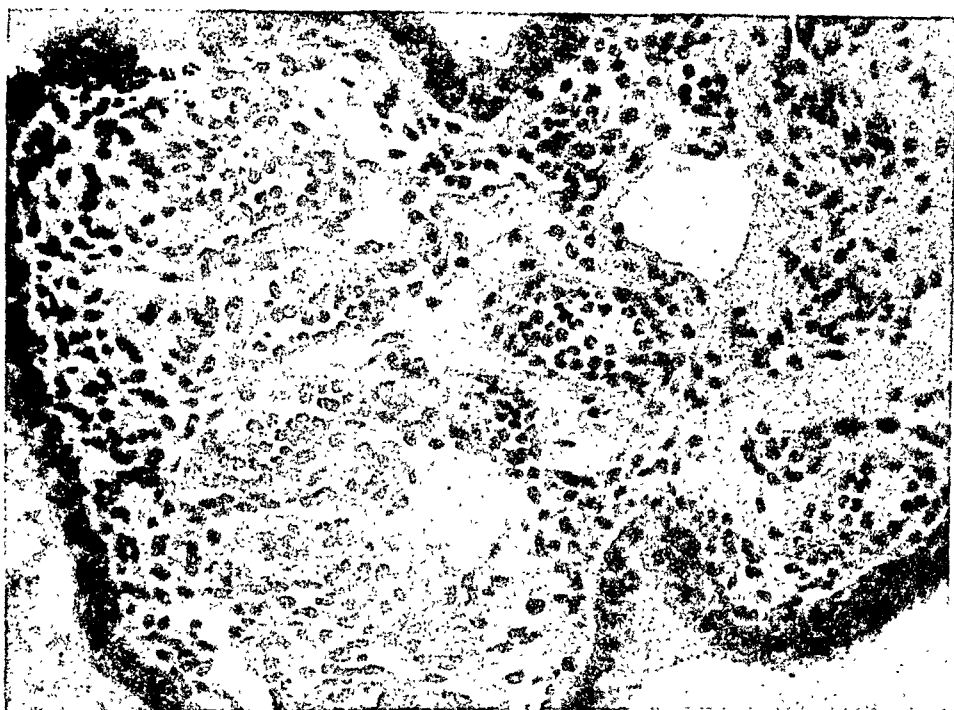


Fig. 3.—Leucostasis. Collections of polymorphonuclear leucocytes are seen in the veins of the tubal rugae.

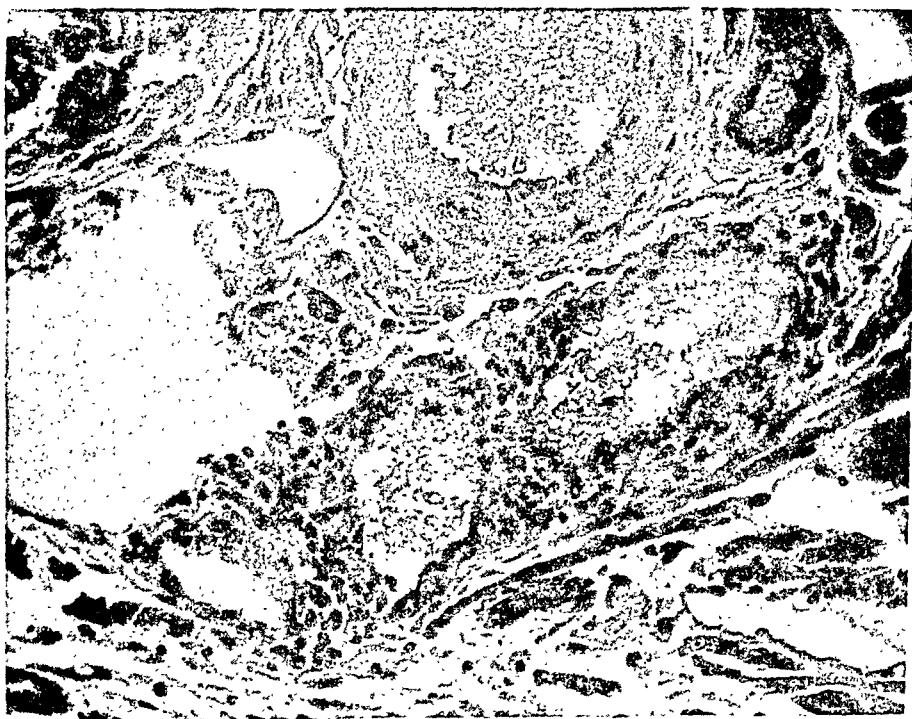


Fig. 4.—Perivascular round-cell infiltration. There is a cuffing of the lymphocytes around the veins of the muscularis.

intrauterine pregnancy in 12 per cent of tubes removed within sixty-five hours of delivery. These authors thought that this high incidence had a racial relationship for it showed a much greater frequency in "the Hawaiian, or part Hawaiian," than in the Caucasian. The incidence in the present series is about half that of Tilden and Winstedt's for the same period of the puerperium. As one would expect, Table V shows that the presence of decidua is related to pregnancy and the early postpartum period. The decidual cells in all but one of the cases occurred in the stroma of the rugae. In no instance was the tubal epithelium involved, but it always appeared as a thin layer of cells covering the decidual bud (Fig. 6). Often, isolated tips of rugae with decidual change appear. These have a vague resemblance to immature placental villi and are often so called by inexperienced observers (Fig. 7).

TABLE IV. THE OCCURRENCE OF TUBAL EDEMA IN 715 PUERPERAL STERILIZATIONS
DISTRIBUTED ACCORDING TO TIME OF OPERATION

DAYS POST PARTUM	STERILIZATIONS	EDEMA ONE TUBE	EDEMA TWO TUBES	PER CENT EDEMA
0	165	4	0	2.4
1	178	9	7	9.0
2	158	2	0	1.3
3	90	3	0	3.3
4	48	1	0	2.1
5	24	3	0	12.5
6	11	1	0	9.9
7	13	1	0	7.7
8	4	0	0	0.0
9	5	0	0	0.0
10+	19	0	0	0.0
Control	46	0	0	0.0

TABLE V. THE OCCURRENCE OF TUBAL DECIDUA IN 715 PUERPERAL STERILIZATIONS
DISTRIBUTED ACCORDING TO TIME OF OPERATION

DAYS POST PARTUM	STERILIZATIONS	DECIDUA ONE TUBE	DECIDUA TWO TUBES	PER CENT DECIDUA
0	165	7	2	5.5
1	178	8	1	5.1
2	158	7	2	5.7
3	90	3	0	3.3
4	48	2	0	4.2
5	24	2	0	8.3
6	11	0	0	0.0
7	13	0	0	0.0
8	4	1	0	25.0
9	5	0	0	0.0
10+	19	0	0	0.0
Control	46	0	0	0.0

TABLE VI. THE OCCURRENCE OF RARE TUBAL FINDINGS IN 715 PUERPERAL STERILIZATIONS

PATHOLOGIC FINDING	NUMBER
Walthard cell rest	12
Cystic Walthard cell rest	4
Lymphangioma	1
Venous thrombosis	3
Endometriosis	17

The rarer findings are listed in Table VI. Walthard cell rests, either solid or cystic, appeared sixteen times. These were often multiple and are quite typical of such rests found elsewhere, as in the ovary (Fig. 8). There was one



Fig. 6.—Decidual reaction.



Fig. 7.—Decidual reaction.

lymphangioma, as illustrated in Fig. 9. These are small, well-demarcated tumors of the tubal muscularis. They are probably extremely rare because less than twenty have been reported in the literature.⁵



Fig. 10.—Venous thrombosis. This is a fairly old process as shown by the discoloration and partial organization of the thrombus

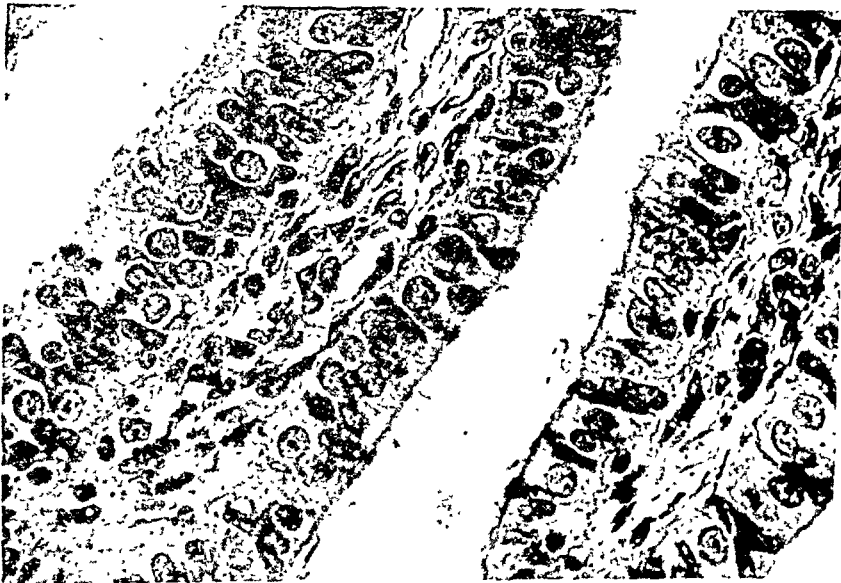


Fig. 11.—Postpartum mucosa. Note the rather high epithelium with evidence of secretion and extrusion of nuclei.

Venous thrombosis of the muscularis was present in three patients (Fig. 10). The thrombi were all similar and showed obvious discoloration and partial organization, all of which indicated that they antedated delivery by several days at least. Such thrombi must originate in varicosities of the mesosalpinx and may account for some of the unexplained emboli associated with labor and delivery.



Fig. 8.—Walthard cell rest.



Fig. 9.—Lymphangioma.

the tubal segments from 17, or 22.4 per cent of the 76 cases. This finding would suggest that patients sterilized early in the puerperium would be less apt to show morbidity during their poststerilization convalescence than those operated upon during the later days of the puerperium. Indeed, Dr. Hellman has told me that this was true in his series of cases, but that he was not able to determine that these patients whose tubes showed acute salpingitis were the particular ones who exhibited postoperative morbidity. Whitacre, on the basis of clinical observation, plus the fact that of 100 intrauterine cultures taken during the puerperium only 13 were sterile, and that these 13 were all taken during the first few hours following delivery, has concluded that if postpartum sterilization is to be done, it should always be done in the first few hours following delivery.

Whitacre's bacteriologic findings would suggest that the observed salpingitis is probably of infectious origin. It seems to me, however, that it might very well be a noninfectious inflammation extending from the uterine cavity where the necrosis and sloughing of the decidua remnants are always associated with leucocytic infiltration. It is suggested that in a future study small fragments of the tubal segments that are to be subjected to microscopic study also be subjected to bacteriologic culture. It could thus be determined whether or not those tubes which show acute salpingitis have actually been invaded by bacteria.

Finally, the morphology of the tubal epithelium as found by Dr. Hellman in those segments of tubes removed at cesarean section or immediately after delivery coincides with that described by Dr. Novak and myself, in 1928, as typical of the pregnant state. The epithelium presented as typical of that from tubes removed from the seventh to the tenth days post partum corresponds most closely with that found by Dr. Novak and myself in tubes removed at the midinterval of the menstrual cycle. Since most patients do not menstruate for six weeks or more following delivery, one wonders what happens to the tubal epithelium in advancing from this phase to the ones which we recognized as characteristic of the premenstrual and menstrual phases of the cycles. In the regularly menstruating woman, these changes ordinarily occur over a period of approximately two weeks.

DR. CARL HUBER, Indianapolis, Ind.—The present study represents a diligent investigation of the morphology of a large number of tubal specimens obtained during the immediate puerperium. All of these specimens are presumed to be of normal tubes as they were functionally capable of permitting pregnancy and were removed from postpartum patients who showed no febrile morbidity. They should, therefore, be indicative of the changes produced in the tube by pregnancy and delivery. Unfortunately, they do not demonstrate any consistent variation from the normal tube in the nonpregnant woman.

These observations would suggest: 1. The endocrine changes in pregnancy do not have an important effect on the appearance of the tube. 2. The mechanical changes produced during pregnancy and delivery do not have any consistent effect on the microscopic structure. This would be anticipated as the tube following completion of the puerperium is normally unchanged both microscopically and functionally.

Of the variety of structural variations described, only the appearance of decidual reaction in the tubal mucosa would seem to be entirely characteristic of pregnancy. This appears in only a small percentage of the tubes examined and, as is well recognized, is not the only extrauterine site where it may be found.

The other conditions which may logically be related to pregnancy and the puerperium are edema, leucostasis, and perivascular round-cell infiltration. They seem to be of doubtful significance and far from constant. They may well be related to the regressive changes which are occurring in adjacent structures and to mechanical variations in the vascular supply of the pelvic organs, as the result of termination of the pregnancy.

It is suggested from the report that bacterial invasion of the tubes is not a frequent finding following normal delivery, in comparison to the bacterial invasion of the uterine cavity which quite normally does occur.

I believe that we are indebted to the author for his description of the morphology of the puerperal tube. There has previously been a gap in our exact information concerning this phase.

The tubular epithelium was almost uniformly low at term, confirming the previous reports of Snyder,⁶ Novak and Everett,⁷ and Tietze.⁸ The low epithelium rapidly increases in height and between the seventh and tenth postpartum day the epithelium is uniformly high. The "secretory" cells are level with the ciliated variety. Extrusion of nuclei is present (Fig. 11).

Conclusions

From a study of 715 pairs of Fallopian tubes, obtained at tubal sterilization on various days of the puerperium, the following conclusions are reached:

1. Acute salpingitis of nonspecific origin and in mild to moderate degree, occurs in one of every three puerpera, approximately between the sixth and eighth days, but is rare during the first four days.
2. Leucostasis may be observed in about 20 per cent of cases during the first twenty-four hours of the puerperium and in about 10 per cent during the second and third days, but is rare thereafter.
3. Perivascular round-cell infiltration, while present both in the pregnant and control groups, is definitely more frequent at term and in the first week of the puerperium.
4. Tubal edema is more prevalent at term and in the first week of the puerperium than at other times.
5. Decidual reaction has its most frequent incidence at term and in the early days of the puerperium, about 5 per cent of cases showing it at this time.
6. Scattered instances of Walthard cell rests, venous thrombosis, and one case of lymphangioma are reported.
7. There is a rapid change in the tubular epithelium from a low to a high secretory phase during the first week of the puerperium.

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Discussion

DR. HOUSTON S. EVERETT, Baltimore, Md.—Dr. Hellman's paper consists of the presentation of carefully observed facts, concerning which it may be presumed that there are no grounds for disagreement or controversy. He has made little or no effort to interpret the significance of these observations. From the discussor's point of view, therefore, the only opportunity presented is to attempt to postulate interpretations of some of the more interesting of the observed facts, and perhaps to suggest further lines of investigation designed to throw more light upon such postulated interpretation.

To me, the most interesting of the observations is the high incidence of acute salpingitis in those segments of tubes removed during the later days of the puerperium. Some of the individual day groups are too small to be of percentage significance. If, however, we condense Dr. Hellman's Table I, we find that, of 539 cases in which the tubes were removed during days 0 to 4 inclusive, only 13, or 2.4 per cent, showed acute salpingitis. In contrast, of the group subjected to operation during days 5 to 10 inclusive, acute salpingitis was found in

OVARIAN PREGNANCY*

With a Report of Three Cases

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OVARIAN pregnancy is one of the rarest forms of extrauterine pregnancy, only primary abdominal pregnancy being encountered less frequently. According to Williams,⁴ ovarian pregnancy was first described in the seventeenth century by Mercerus and St. Meurice. It was regarded as a real, though rare, possibility until Velpeau in 1835 expressed skepticism concerning many of the previously described specimens and doubted if it could occur at all within the substance of the ovary. While most German authors have admitted its possible occurrence, English and American authors in general denied its possibility until 1899, when Tussenbroek³ gave an accurate description of one, to be followed three years later by the report of the first one described in this country, by Thompson² in 1902. Today, any discussion as to the possibility of its occurrence is of only academic interest, and numerous examples of undoubted authenticity have been presented in the literature.

It is of importance, of course, that certain criteria be observed in deciding whether a particular case actually does represent a true ovarian pregnancy. Those criteria formulated by Spiegelberg¹ in 1878 are the ones which are accepted as being the "sine qua non" before a particular pregnancy may be regarded as a true ovarian pregnancy.

In regard to the mode of origin of an ovarian pregnancy, some facts are known, while other factors involved offer an interesting field for speculation and are as yet unsolved. When we recall that complete maturation of the ovum is necessary before fertilization can occur, it becomes obvious that, for a pregnancy to take place in the ovary, there must be a variation from the usual course of events. While the first polar body may be extruded from the ovum while still within the ovary, the second polar body is ordinarily not cast off until the ovum is expelled from the follicle. If on occasion, however, maturation of the ovum is completed while the ovum is still in the follicle with the latter ruptured, a sperm cell could enter, fertilize the ovum, and the pregnancy begin in situ. Robert Meyer, on the other hand, believed that most often a cortical implantation of the ovum occurs with later invasion of the ovarian stroma. Novak states that, after its discharge, the ovum may be fertilized and then be implanted in the follicle or corpus luteum (intrafollicular implantation), the trophoblast soon penetrating these and invading the deeper structures (juxtafollicular implantation). Probably any of these mechanisms may occur, but only if one had

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

DR. HELLMAN (Closing).—In reply to Dr. Everett, I would say that we were disappointed that we could find no correlation between the microscopic finding of an acute salpingitis and an acute febrile postoperative course. However, the later one waits to perform this operation, the more likely one is to find a febrile course.

In regard to the high epithelium that Dr. Everett mentioned, we are now carrying on further studies. We are actually measuring the height of the tubal epithelium at various days of the puerperium, to see whether this rapid growth is connected with lactation. Also, the oxygen requirement of the tubal mucosa changes with the menstrual cycle, and studies are being carried out on the metabolism of tubes at various stages of the puerperium.

Dr. Huber has reviewed our findings excellently. It is true that leucostasis is found to some extent in normal tubes. However, there is a greater frequency in pregnancy and therefore that was stressed in this paper.

CASE 1.—V. S., unit No. 104482, aged 29 years, para ii, was admitted to Strong Memorial Hospital on July 8, 1935. Her past history is irrelevant except for two normal, full-term pregnancies and two miscarriages. The last menstrual period began May 22, 1935, and was normal. On June 22, 1935, daily "spotting" began and continued until July 3, when a more active flow began, accompanied by crampy lower abdominal pain. The day after admission, she expelled some tissue which on examination was found to be decidua. Her symptoms subsided and she was discharged. No demonstrable mass was noted on pelvic examination at the time of discharge and she was regarded as a complete abortion. She was readmitted two weeks later, on August 1, 1935, with recurrence of right-sided lower abdominal



Fig. 2.—Early chorionic villi, detached and lying in the clot noted in Fig. 1. ($\times 100$)

pain but no bleeding. Her general condition was good: temperature 38°C .; pulse 90; blood pressure 115/72. The red blood cells 4,100,000, hemoglobin 11 Gm., and white blood cells, 9,000. Abdominal examination revealed some tenderness and slight spasm in the right lower quadrant, while on pelvic examination, a sensitive, semicystic mass about 6 cm. in diameter was found to the right of the uterus. A diagnosis of ectopic pregnancy was made and operation carried out. On opening the abdomen, no free blood was encountered. The right appendages were somewhat adherent and included a small mass of attached blood clot. The right tube and ovary were removed; also the appendix. Her convalescence was uneventful.

Description of Specimen.—The right tube was grossly normal. The right ovary measured 5 by 5 by 4 cm. and was partially covered by adherent blood clot. On bisecting the ovary, a well-developed corpus luteum was observed in one pole of the ovary, while adjacent

the extremely good fortune to encounter an ovarian pregnancy in the very early stages, could one provide an accurate answer to these questions.

The symptoms and findings on examination are those common to ruptured tubal pregnancy and may be slight, making diagnosis difficult, or may be severe with profuse intra-abdominal hemorrhage. Rupture may be early but, generally speaking, it is likely to occur rather later than is the case in tubal pregnancy. A positive diagnosis cannot be made until the abdomen is opened and the involved structures removed for study.

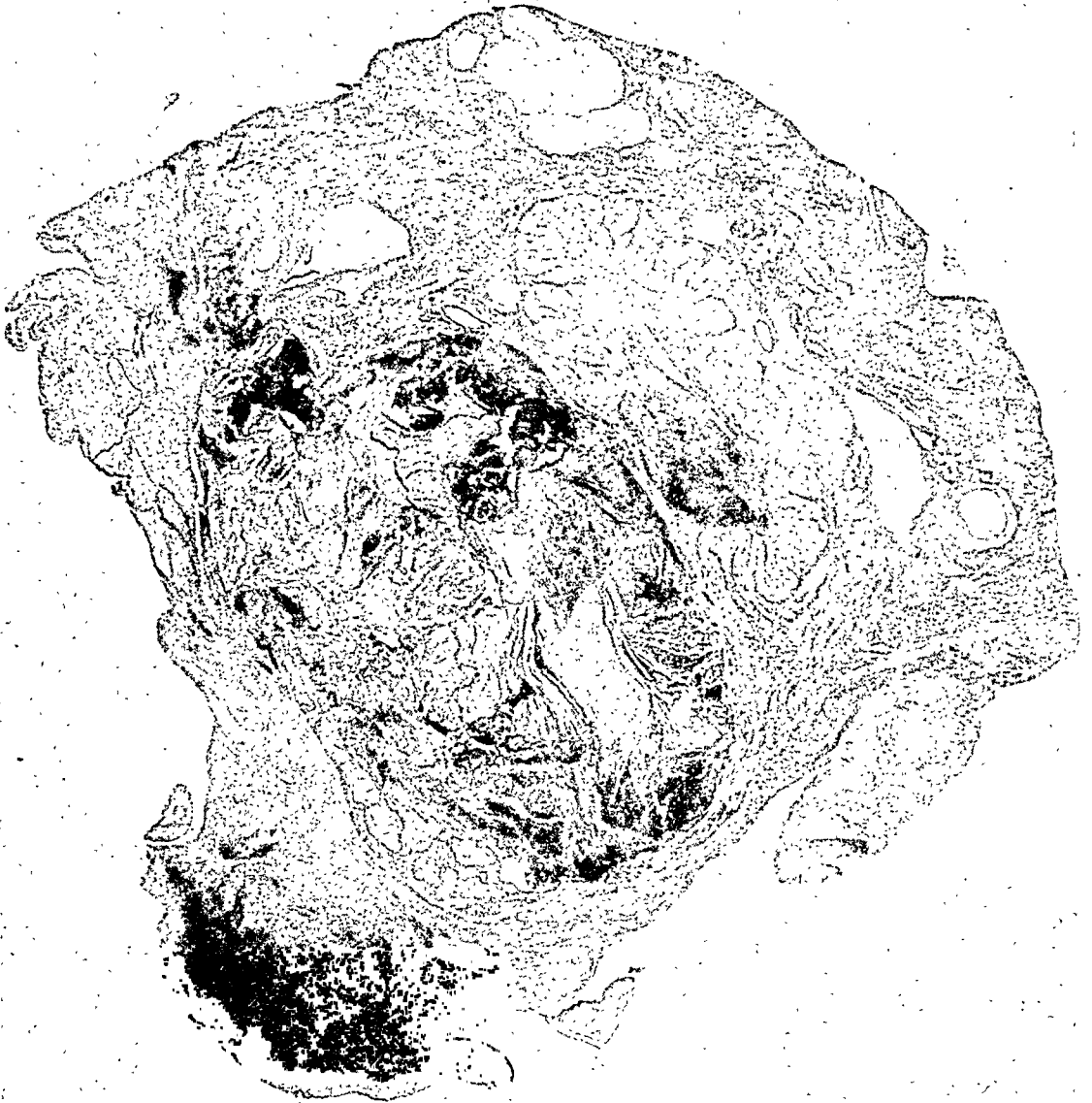


Fig. 1.—A cross section of the whole ovary from Case 1, under low magnification ($\times 6.5$). Note the large clot containing the pregnancy and the adjacent corpus luteum—juxtafollicular implantation.

In spite of its rarity, we have had the opportunity of observing three examples of ovarian pregnancy, all of which satisfactorily fulfill the criteria as laid down by Spiegelberg. These three cases occurred in a series of 224 of the various types of extrauterine pregnancy.

menstrual period occurred from January 27 to February 3, her previous menstrual period having occurred on December 25. She began to have intermittent episodes of rather severe left lower quadrant pain on January 18 and these continued at intervals until admission.

On admission, temperature was 37° C., pulse 98, blood pressure 109/78. The red blood cells, 4,100,000, hemoglobin 13 Gm., and white blood cells 13,000. Abdominal examination showed marked tenderness and spasm in the left lower quadrant. Pelvic examination revealed an exquisitely sensitive cystic mass at the left of the uterus whose dimensions could not be easily outlined on account of the marked tenderness. A diagnosis of ruptured ectopic pregnancy was made and operation carried out by Dr. C. A. Elden.

On opening the abdomen, considerable dark blood was encountered. The sigmoid, omentum, and small bowel were adhered to the left appendages. After freeing them, the left tube and ovary were removed; also the appendix. The convalescence was uneventful. This case presents an unusually early rupture of an ovarian pregnancy.



Fig. 4.—A low-power ($\times 7.5$) magnification of a segment of the ovary in Case 2. Note the clot adjacent to the corpus luteum and compressing it on one side. Another example of juxtafollicular implantation.

Description of Specimen.—The left tube was somewhat enlarged but intact. The ovary was a cystic structure 6 cm. in diameter with a small jagged rupture, 1.5 cm. in diameter, in its posterior aspect. On opening the specimen further, a well-developed corpus luteum was found and adjacent to this, and embedded in the ovarian stroma, was a larger mass of clot 4 cm. in diameter.

On microscopic examination, the findings were quite comparable to those described in Case 1. The corpus luteum was intact, but was markedly compressed in its lower side at the point adjacent to the blood clot, from which it was separated by a thin layer of connective tissue. The lutein cells were undergoing degenerative changes. At this point, too, a few trophoblastic cells were seen intermingling with the lutein cells but there had been no active destruction of lutein cells by the few invading fetal cells. Embedded in the clot were numerous well-formed early chorionic villi. Ovarian tissue was demonstrable, covering the remainder of the clot except at the point of rupture. No decidual reaction was noted. No trace of an

to this is a mass of old blood clot which appears to be surrounded by a thin, membranous structure. This mass measured 2 by 2½ cm. in diameter. What grossly appears to be ovarian tissue surrounds both the corpus luteum and the small mass of clot. On microscopic study, the well-formed corpus luteum is observed, though the cells are undergoing degenerative change. Adjacent to this, but definitely separated from it, is the mass of clot, embedded in the substance of the ovary and in which a number of early chorionic villi are seen. Most of them lie loose in the clot, but an occasional villus is found attached to the margins of the sac, fastening villi. No trace of an embryo was found. A layer of undamaged ovarian tissue is demonstrable throughout the specimen except at one point which probably represents the site of rupture. No decidual reaction is noted. Numerous sections through the tube showed it to be anatomically intact, but did show some degree of chronic inflammatory reaction. (Figs. 1, 2, 3.)

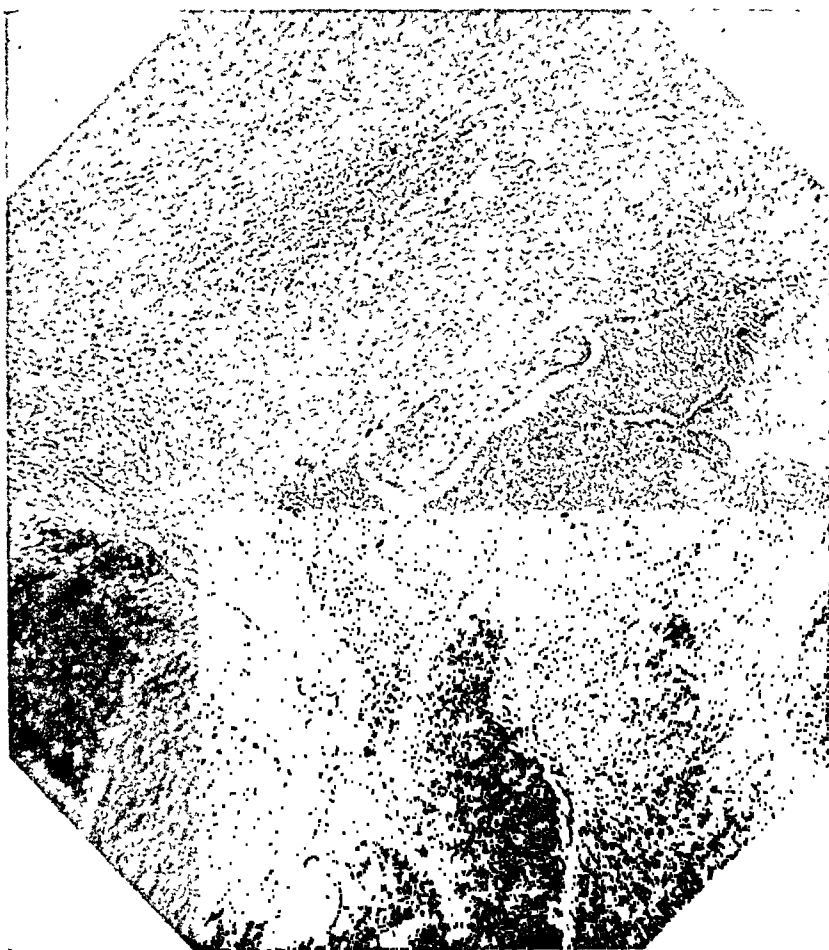


Fig. 3.—Two fastening villi attached to the wall of the sac, which is ovarian tissue. (Case 1.)
(x100)

It is interesting to speculate, but one can only speculate, on the mode of implantation here: The fact that the corpus luteum is undamaged by any invasion of trophoblast, while the site of the pregnancy lies beneath this, probably means a rapid invasion of the stroma of the ovary after fertilization had occurred, with no interference to the development of the corpus luteum—juxtafollicular implantation.

CASE 2.—M. A., unit No. 161938, aged 30 years, was admitted to Strong Memorial Hospital on Feb. 4, 1940, under the care of Dr. C. A. Elden. Her past history is irrelevant except for the occurrence of two normal, full-term pregnancies. What she described as a normal

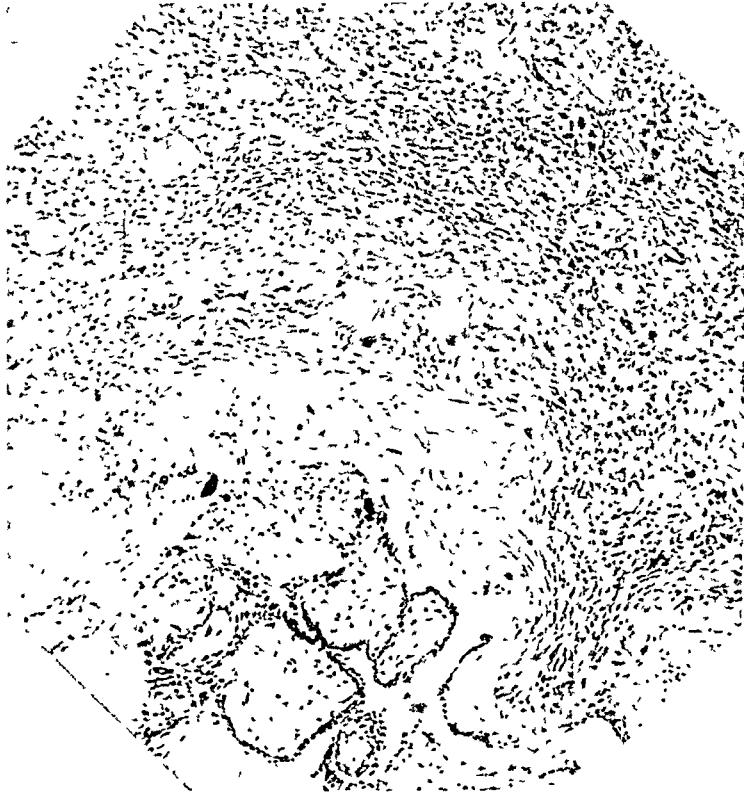


Fig. 6.—Early chorionic villi embedded in the substance of the ovary in Case 3. Note also the rather active invasion of ovarian stroma by trophoblastic cells. ($\times 100$)

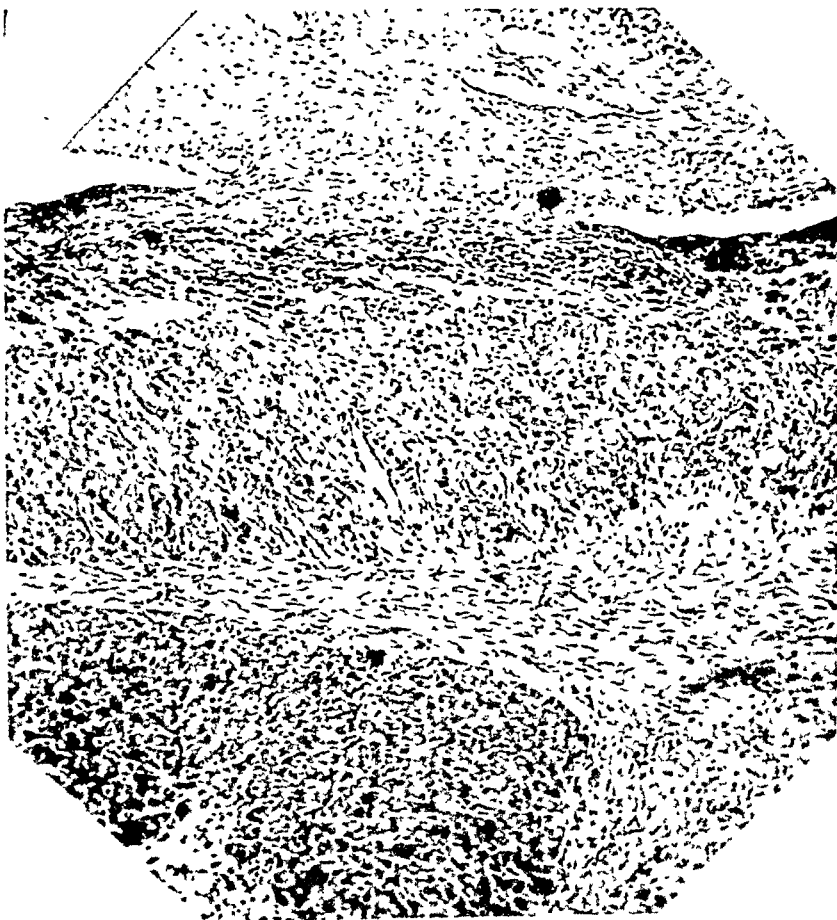


Fig. 7.—A portion of the corpus luteum near the pregnancy but not in such close proximity as in the other two cases. ($\times 100$)

embryo was seen. Numerous sections of the tube showed it to be intact but a chronic inflammatory reaction was found. The mechanism of implantation and development in this pregnancy were probably identical with those occurring in Case 1. (Figs. 4, 5.)

CASE 3.—M. F., unit No. 190991, aged 34 years, was admitted to Strong Memorial Hospital on April 9, 1947. Her past history is irrelevant except for the occurrence of two normal, full-term pregnancies, five and two years previously. Her last menstrual period occurred on March 14, 1947. The night before admission, she had an episode of acute lower abdominal pain with onset of slight vaginal bleeding. On admission, she was in a state of mild shock. Blood pressure 100/60, temperature 37° C., pulse 54, and white blood cells 6,000.



Fig. 5.—Early chorionic villi embedded in the clot adjacent to the corpus luteum in Case 2. ($\times 100$).

Examination revealed an acutely inflamed abdomen, with signs of internal hemorrhage. On pelvic examination, a cystic bulging mass was felt in the posterior cul-de-sac. A diagnosis of acute ruptured ectopic pregnancy was made and immediate operation carried out, a transfusion of 1000 c.c. of whole blood being begun at the same time. When the abdomen was opened, a large amount of old and fresh blood was encountered, at least 1000 c.c. The right appendages were found to be normal as was the left tube, but the left ovary was somewhat enlarged and, on its outer aspect, presented a dark cystic area about 1.5 by 2 cm. in diameter. In the lateral region of this was a small rupture through which free bleeding was occurring. The left tube and ovary were removed. Her convalescence was uneventful.

Description of Specimen.—The tube was intact and grossly appeared quite normal. The ovary measured 4 by 2.5 by 2 cm. On one side was a rent through which a fragment of blood clot protruded. When the ovary was bisected, a clot 2.5 by 1.5 cm. was found immediately under the surface; also a small follicular cyst adjacent to this. The ovarian stroma was

It has been suggested that speedy and adventuresome spermatozoa may leave the tube and rush through the follicular breach successfully to attack the lingering ovum. This postulate would be difficult to substantiate.

The second, or reduction division of chromosomes that Dr. Wilson has mentioned, usually takes place some time after the first phase of myosis, that produced the first polar body just before follicular rupture. This first myotic division results from only a longitudinal split, not the necessary numerical halving of the chromosomes which occurs probably in several hours. When the follicle ruptures, as it must if spermatozoa are to enter, fluid is released, pressure diminished, the granulosa is partly disrupted and, inevitably, hemorrhage into the antrum occurs before myosis could be completed. Now the enzyme, hyaluronidase, produced by spermatozoa, must be at least an adjunctive agent for dispersal of the corona radiata, for there is hyaluronic acid among the granulosa cells investing the egg. An antihyaluronidase factor has been found in the blood serum of various species. Other enzymes may be essential to the penetration of the vitelline membrane and, for them, too, there may be in the blood inactivating factors. At all events, fertilization in vitro of rabbit and human eggs has not been achieved in the presence of blood, and preliminary experiments by Finkle at the Free Hospital for Women tend to show that if there is blood in the rabbit tube fertilization in vivo fails. I think this would likewise be the case within the human follicle.

Meyer's and Novak's explanation of ovarian pregnancy is easy to accept. Sperm do not live long in peritoneal fluid. It seems likely that the eventually ectopic ovum finds temporary shelter and spermatie service within, at least, the protective fimbriae of the tube. After activation by the sperm, a failure of tubal peristalsis (for the ciliary current must be a weak force as applied to the bulky ovum) leaves the zygote where it is or reverse peristalsis ejects it.

Dr. Wilson notes that no decidua was found in his specimens. By several workers, Runner, Fawcett, Wislocki, Waldo, and Nicholas, transplantation to the eye, the kidney, even onto the peritoneum of mouse eggs fertilized in vivo has shown that access to nothing more than circulating blood will permit trophoblastic growth. Study of normally implanted conceptuses leads one to suspect that the trophoblast seeks, not primarily decidua, but maternal blood. In the late secretory endometrium, the substantial stroma gives support to the vascular sinusoids, the endothelial cells of which readily submit here and there to engrossment by the syncytium.

I believe it likely that so long as the integrity of invaded maternal vessels and adaptive sinuses containing good blood is maintained by surrounding tissues and the site of entry plugged by the trophoblast, conceptual growth continues. When available blood is deficient or becomes insufficient for the rapidly growing normal "neoplasm," or the local inadequately buttressed maternal vascular system ruptures, abortion occurs. The reason, perhaps, why, as Dr. Wilson points out, an ovarian pregnancy progresses further than the tubal variety is because of the greater expansion-potential of the more elaborate and more firmly supported blood supply of the ovary, beneath the cortex of which the phagocytic syncytiotrophoblast succeeded in imbedding the conceptus.

DR. JOHN I. BREWER, Chicago, Ill.—The three specimens are of extreme interest because the ovaries containing the pregnancies were only slightly enlarged. The relationship of the ovarian structures and the implantation sites can therefore be determined. The embryonic mass is not within the corpus luteum and there is not the least suggestion that it had been previously. Those trophoblastic elements that are intermingled with corpus luteum tissue are obviously invading the corpus luteum from without. In larger and older specimens in which the relationships are more disturbed, it is impossible to draw conclusions. Confusion in interpretation also may result from failure to differentiate decidual tissue in the ovary from corpus luteum tissue.

It is logical to assume that implantation phenomena are fundamentally similar in an ovarian pregnancy and in a pregnancy in the endometrium. Implantation is on the surface. The embryonic mass enters the maternal tissue and becomes buried. No evidence of surface

greatly thinned out around the clot and a small corpus luteum was observed. A small membranous sac measuring 4 mm. in diameter was found embedded in the blood clot and may have represented fetal membrane, but no gross embryo was seen. On microscopic study, a fragment of the chorionic membrane to which early villi were attached was found embedded in the clot, also numerous other normal-appearing early villi which had been broken off from their attachments.

Adjacent to part of the clot, but in the ovarian stroma, was an irregular fibrinous layer, suggestive of Nittabuch's fibrin layer as seen in uterine implantation. There was also some invasion of the ovarian stroma by trophoblastic cells. The corpus luteum was well developed but was broken on one side, apparently the result of trauma incidental to the rupture of the sac. Nothing suggesting a decidual reaction was noted in any of the slides studied. (Figs. 6, 7.)

Summary

Three examples of ovarian pregnancy are presented, each of which fulfills the criteria necessary for making such a diagnosis. From the clinical standpoint, one of them presented a diagnostic problem, while the other two presented findings which readily permitted a diagnosis of ectopic pregnancy, and one was an extremely acute case, with extensive intraperitoneal hemorrhage. Cases 2 and 3 represent an unusually early rupture. Study of the specimens revealed in two of them well-developed corpora lutea adjacent to the pregnancy, the so-called juxtafollicular implantation, but whether this was preceded by fertilization in the actual follicle or on the surface of the ovary, it is, of course, impossible to say at the present time. The well-developed and intact corpora lutea so close to the pregnancy rather suggest fertilization in the follicle, followed by rapid invasion of the underlying ovarian stroma. In none of the specimens was any decidual reaction noted.

The fate of the ovum in ovarian pregnancy is comparable to that which takes place in other forms of extrauterine pregnancy; namely, development for a period of time, with associated erosion of the adjacent tissues and eventual rupture, with sometimes slight and sometimes severe symptoms. While we have not encountered an example, it is interesting to note that a higher percentage of ovarian pregnancies proceed to term than is the case with tubal pregnancy, this being no doubt due to the more resistant type of tissue in which the pregnancy is embedded.

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Discussion

DR. JOHN ROCK, Brookline, Mass.—Dr. Wilson calls our attention to an intriguing disturbance of reproductive physiology. Symptomatology, diagnosis, and treatment, as Dr. Wilson says, are those of ectopic gestation in general.

To the biologist it may seem possible that an entrapped ovum cleaves and develops parthenogenetically. Autogenous ovular growth is found in several forms that are, at least schematically, lower among animals than we are. Clinical histories are so heartlessly intrusive and so shamelessly published, they would surely have adorned Christian medical literature with more than one case of virginal gestation if parthenogenesis could explain ovarian pregnancy.

OBSERVATIONS ON THE ROOMING-IN PROGRAM OF BABY WITH MOTHER IN WARD AND PRIVATE SERVICE*

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ON JULY 12, 1947, the policy of rooming the normal, full-term, newborn baby with its mother was inaugurated in the obstetric wards of the Jefferson Medical College Hospital. From that time until April 12, 1948, which represents the period covered by this study, 1,018 newborn babies were cared for in this fashion. Of these, 926 were the offspring of ward patients; 92 were the babies of private patients who were cared for in a low-cost, semiprivate ward. While the obstetric wards, which were built some twenty years ago, were originally planned with no thought of such a project, yet actually the architectural arrangement lent itself quite well to this undertaking and it was found unnecessary to make any physical alterations.

The ward service consists of six rooms, each containing six beds. Each of the wards has its own bathroom, each has its own wash basin quite accessible within the ward space (Fig. 1). The rooms are ordinarily well heated, and the windows are protected by ventilators. In addition to the six wards for obstetrical patients, there is a labor room of four beds, a nursery for full-term babies, a premature nursery, an isolation nursery, a formula room, a central office, a sterilizing room, service rooms, etc. All of these occupy one floor of the Samuel Gustine Thompson Annex, the wards and nurseries being arranged in a rectangular fashion about a central office. There is free visibility from the corridors into the rooms and from one ward to another by glass windows. The nurses, residents, internes, student clerks, etc., circulate rather constantly through the various parts of the floor so that mothers and babies are under frequent observation during the day, and not infrequent observation at night.

Procedure

Babies are kept in cribs at the mother's bedside both day and night unless one or the other is ill, or unless at night an individual baby is unusually noisy.

At first, the equipment for the care of the mother's breasts and of the baby was placed on a central table in each ward but it was soon observed that this arrangement would permit of cross-infection, and was also inconvenient to mother and nurse. In order to overcome this difficulty, a small crib-wardrobe was designed which the hospital carpenter constructed and which is hung on the end of each baby's crib. The crib-wardrobe consists simply of an upper and lower shelf. The top shelf contains covered jars for alcohol sponges, water sponges, dry cotton balls, and used sponges. The larger lower shelf contains the supply of individual diapers, pads, and blankets for a day's usage (Fig. 2).

*Read at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

implantation remains. The sequence of events explains the findings in the described ovarian pregnancy more reasonably than does the supposition of intrafollicular implantation for which there is no evidence and no proof.

Another interesting point for discussion is contained in the history of the first patient. The patient was discharged from the hospital after she had passed some tissue from the uterus which on examination was decidua without chorionic tissue. The symptoms had also subsided. The diagnosis was a complete abortion. Subsequently the extrauterine pregnancy was proved.

The finding of decidual changes in the endometrium without chorionic tissue suggests an extrauterine pregnancy. All efforts should then be made to make such a diagnosis. There are exceptions to this rule, of course. (1) Chorionic tissue may be missed because the entire specimen is not available for examination. (2) The few microscopic sections that are usually made of a given specimen may not include the chorionic tissue. (3) The entire trophoblast may have been aborted prior to the time the specimen is obtained for examination. (4) Decidua may be present without pregnancy. TeLinde described several such instances. One patient of ours had metrorrhagia and menorrhagia of six years' duration. A dilatation and curettage was done for diagnosis. The endometrium was proliferative in type and there was no chorionic tissue. Ten weeks later, after a continuation of the abnormal bleeding, the uterus and the corpus luteum were removed abdominally. The endometrium had a well-differentiated decidual reaction. The corpus luteum was regressing. Complete study of the uterus and gross inspection of the tubes and ovaries revealed no pregnancy. Decidual changes in the endometrium have been described in patients with certain ovarian tumors in the absence of pregnancy. Decidual tissue has also been produced experimentally in the human endometrium by prolonging the life of the corpus luteum with chorionic gonadotropin. While it is true that decidua may be present without pregnancy, it is our belief that such is relatively rare. (5) It is possible for an extrauterine pregnancy to resolve spontaneously in rare instances. In such a case, decidua may be obtained from the uterus with no chorionic tissue. The patient gets well and a pregnancy is not proved. With these things in mind, however, the rule still holds that decidual changes in the endometrium in the absence of chorionic tissue strongly suggest the presence of an extrauterine pregnancy.

Absence of decidual reaction in the endometrium does not mean that the patient is not pregnant. Early in a normal uterine pregnancy, decidua may not be present, as Hertig and Rock and we have observed. Early in an extrauterine pregnancy, and in those patients in whom symptoms have been present for some time, there frequently is no decidual tissue in the endometrium.

DR. WILSON (Closing).—Dr. Rock emphasized much more strongly than I did the very complicated process of the implantation of the ovum in the ovary. From the specimens shown, one can only speculate in regard to the mechanism of this. What would be needed to get actual information would be for someone to find a very early ovarian pregnancy that had not yet ruptured. I am not aware of such a one having been reported.

I think the decidual reaction is not important. Of course, if there be any endometrium in the ovary one will get decidua developing in this tissue.

baby care, and emphasizing constantly the importance of cleanliness. The mother is encouraged to move freely in bed and participate in these various activities, but ordinarily she does comparatively little for her baby during the first twenty-four hours other than observe its progress.

By the end of twenty-four hours, the mother is generally out of bed, and thereafter conducts practically all of the routine care of herself and of her baby. She goes to the lavatory, uses the central wash basin, and sits either on the bedside or on a chair by her baby's crib. She calls upon the nurse in case of question or difficulty, but she learns very quickly to manage all ordinary situations and ordinarily gives her offspring excellent attention. From that time on until discharge, the nurses have very little to do with respect to feeding or changing of the baby.

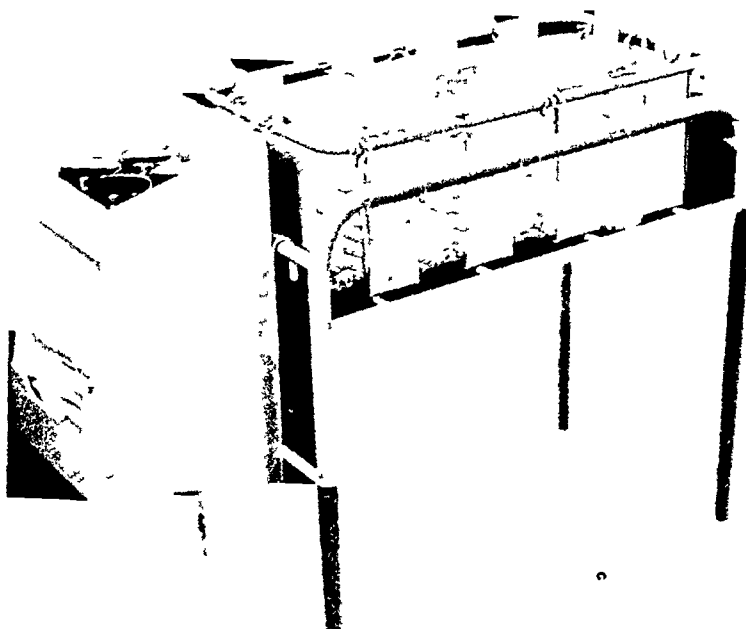
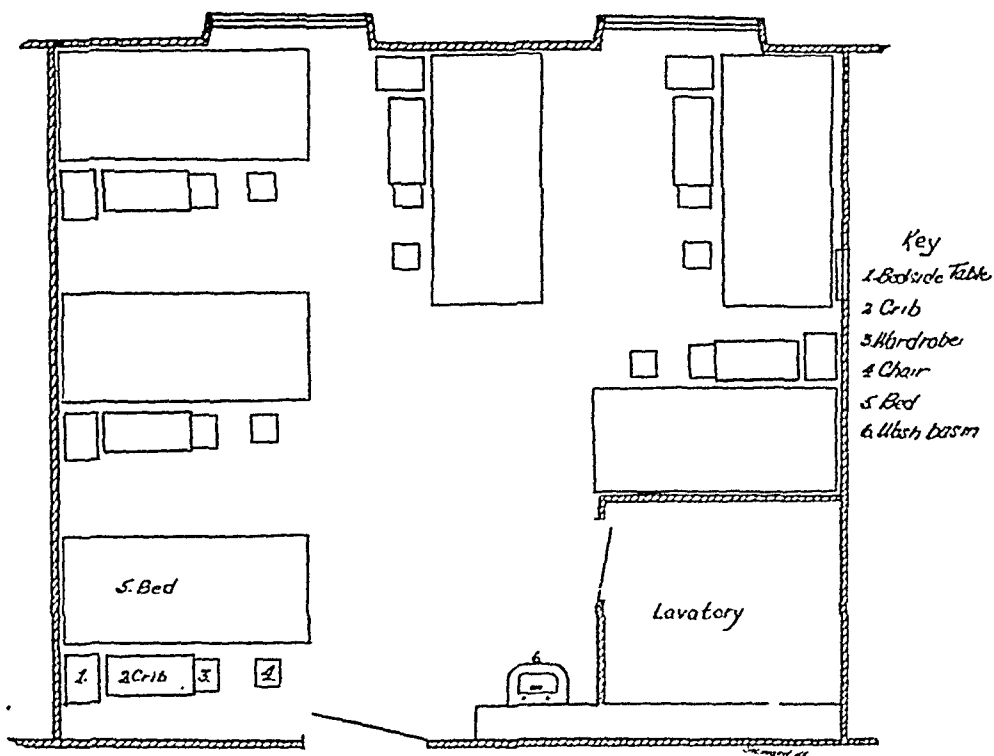


Fig. 2.—Crib wardrobe equipped and attached to crib.

Each morning the mothers are supplied with an individual "bath pack" containing a fresh change of clothing for the baby, fresh materials for the crib, baby blanket, and a sterile sheet of paper for weighing on the scales. Ward rounds are then made by the nurses from the central nursery employing a ward carriage equipped with scales, antiseptics, dressings for the navel, thermometers, and emergency drugs (Fig. 4). As this equipage comes along, the mother undresses her baby on her bed, changes the linen in the crib, puts the sterile sheet of paper on the scales, and watches her baby being weighed. She also watches the cord dressing changed and is instructed in the cleansing of neck, axilla, groin, vulva, with sterile swab and sterile water. Most mothers, even multiparas, are surprised and rather concerned at the presence of the stump of umbilical cord, never having noted it before in the course of baby care. Upon the occasion of these morning rounds, the nurses make their records of the baby's weight and temperature, and obtain from the mother's record of the previous twenty-four hours the data concerning nursing periods and baby's bowel movements. Twice in the course of her eight hour duty, the graduate in charge of the nursery makes rounds and personally checks on all babies. In the meantime, the babies are under almost constant observation of the floor nurses.

With this arrangement, the mother can readily reach her baby and the materials for its care while she is lying in bed or sitting on the edge of the bed; and no one touches these materials except herself (Fig. 3). The wardrobe can be readily lifted from the end of the crib and is constructed without covers or drawers so that it is easily and thoroughly washed with soap and water. This arrangement has worked most successfully, at an expenditure of not more than five or six dollars per crib, and has made it possible for us to provide quite efficiently for the individual care of each baby.



Floor Plan of Six Bed Ward Showing Beds and Cribs in Place

Fig. 1.—General plan of a 6-bed ward room.

Healthy, normal, full-term babies are placed with their mothers very soon after delivery. If the baby has considerable mucus in its pharynx, it is kept in the central nursery until this has cleared and respiration is normal. If the delivery is during the night, the baby may not be placed with the mother until the next morning. In not a few instances, however, the baby is at the mother's bedside within two to three hours after delivery. The practice is for the attendant in the delivery room to call the ward nursery when a delivery is completed and the newborn baby's condition determined to be satisfactory by the attending obstetrician. An individual stand, crib, and wardrobe is then prepared and the baby transported by the nursery attendants to its freshly prepared habitation in the nursery. Within a short time, with the exceptions mentioned above, the baby is beside the mother in the ward. Baby and mother are generally ready for this intimate association at an early hour for we employ little sedation during labor, light inhalation anesthesia for delivery, and local anesthesia for episiotomy and repair.

During the first twenty-four hours after delivery, the nurses take a great deal of time with these patients, demonstrating the technique of nursing and of

Mothers are encouraged to nurse their babies. In not a few instances, the baby is put at the mother's breast in the delivery room, as soon as the repair of the episiotomy or laceration is completed, and the parturient has been cleansed and made comfortable. This placing of the baby with the mother seems to be a considerable solace to the wailing newborn infant, gives the mother an excellent chance to see and fondle her newborn, and provides the first instruction in the technique of breast nursing.

Subsequently in the wards the babies are placed on a "demand" feeding regime. Mothers are instructed to nurse their babies for not more than five minutes during the first two or three days and as frequently as the baby seems hungry. In some cases where the baby seems unusually hungry or thirsty, a bottle of sterile lactose water is provided and administered by the mother from time to time. When the milk comes in, the mother then nurses the baby the usual fifteen to twenty minutes, and ultimately the nursing schedule settles down to about every three or three and one-half hours, depending on the requirement of the individual baby.

As the reader may surmise from the foregoing, early activation of the mother and breast feeding on a demand schedule adapt themselves very well to the program of rooming baby with mother; and in turn, the rooming-in program hastens involution and recovery of the mother, and generally stimulates more efficient breast nursing.

Most of our normal parturient ward patients are discharged on the fifth or sixth day post partum. There have been none returned to the department because of delayed post partum bleeding, subinvolution, or birth tract infection.

On the ward service, the husband is permitted to see the baby within an hour after delivery and then visit his wife and baby on two evenings a week. No other visitors are permitted except in case of grave illness or unusual circumstance. All visitors wear gowns while in the wards. The patients in the low-cost, semiprivate ward are permitted to have visitors twice a day, but this includes only the husband and mother of the patient. While visitation is always a problem, when the baby is housed with the mother, the family seems a trifle more understanding and cooperative than when the baby is kept in the central nursery, and the mother—having the companionship of her baby—is less desirous of having a large number of visitors.

Upon discharge, the mother dresses her baby in the presence of the nurse, checks the identification tags, and receives her final instructions, formula, and reference card to the Well Baby Clinic, or private pediatrician.

Reasons for Undertaking the Project

Our principal reasons for undertaking this project were two: first, the fear of contagious disease of the newborn in the central nursery, infectious diarrhea, impetigo, and respiratory infection. Unfortunately, we have had our share of these in Philadelphia and other cities of Pennsylvania, and the memory of them was fresh in our minds.

The second reason was the impossibility of maintaining a sufficiently large corps of trained nurses to care properly and safely for babies night and day. We could not satisfy our own peace of mind on this score nor could we meet the demand of the Department of Health. The procedures of central nursery care had become so exacting that under the stress of overwork and underhelp, technique would be broken here or there and the whole top heavy structure would collapse.

In addition to these two primary considerations, we were conscious of the fact that the modern hospital routine was separating the baby more and more

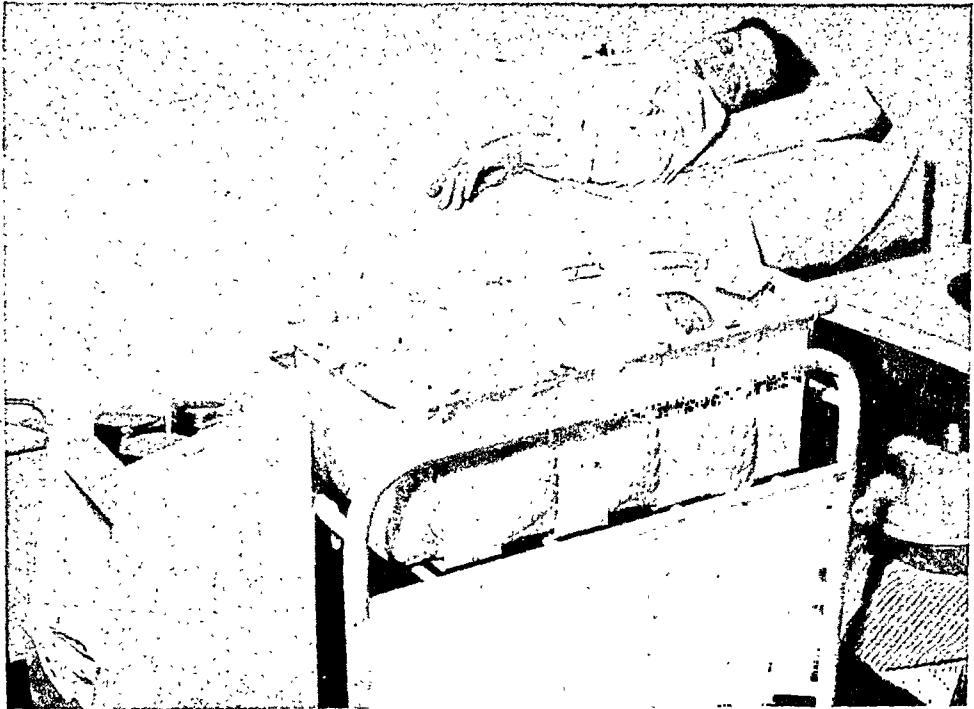


Fig. 3.—Baby and equipment at bedside of mother.



Fig. 4.—Ward carriage equipped for morning baby care.

The most significant observation that has come out of this nurse-patient adjustment is the fact that with the same number of nurses and nursing hours, which under the old system was grossly deficient as regards the regulations of the Department of Public Health and our own desires in the matter, we have been able to set up in the rooming-in plan care which is adequate and very satisfactory.*

Two circumstances have brought about this improvement in care. First, early ambulation has made it possible for the normal parturient to care for herself after the first twenty-four hours, and parenthetically, to benefit by activity and leave the hospital in better condition than ever before.

Second, the rooming-in plan has made it possible for normal parturients to take over the routine care of the normal full-term baby soon after delivery. With this arrangement, nursing care is concentrated upon the ill mother, the recently born baby, the premature baby, for all of whom the hours of nursing care have been built up to an adequate level.

With the mothers participating, the hours of observation and individual care of the normal full-term baby have been increased to practically twenty-four hours in the twenty-four, and the attention given to the baby by its own mother during the twenty-four hours is as meticulous as that which would be rendered by a graduate nurse assigned to each individual baby. (Speaking for myself [Montgomery] I may say that for the first time in many years I can see a solution for the problem of adequate supervision and care of the newborn in hospital practice.)

Breast feeding is an important part of the rooming-in of baby with mother. The procedures of bedside care are naturally simplified by the mother's nursing the baby, and the demand schedule of nursing has effected earlier and steadier weight gain. The presence of the baby in the room also seems to arouse a desire to breast feed the baby in patients who had been reluctant to do so. Eighty-three per cent of the ward patients have been nursing their babies in whole or in part on the fifth or usual day of discharge, and twenty-five per cent of their babies have regained their birth weight by this time. Fifty to sixty per cent of the patients in the low-cost, semiprivate rooms nurse their babies.

As to the persistence with which this breast feeding was continued, the following data are available: Of 689 babies discharged between September, 1947, to February, 1948, 335, or roughly 50 per cent, were brought to the Well Baby Clinic of the Pediatric Department. (The remainder were referred by visiting nurses to neighborhood Public Health Centers.) Of these 335, 52 babies had been placed on a formula in the hospital or had discontinued breast feeding sometime during the first month of life. An additional 26 babies had been kept in the premature nursery for varying periods of time and discharged on artificial feeding. Therefore, of the 209 full-term babies of *this* group followed in our own clinics, 83 per cent were still nursing at the breast for one or more months after delivery.

The last question which arises in connection with the rooming-in project is, how do the mothers like it? How much benefit do they obtain from it? Under the circumstances of the ward service, the patient accepts the regime which is established by the hospital administration unless some peculiar condition necessitates an exception in the individual case. However, most of the ward mothers take to the situation with more interest and enthusiasm than a mere compliance. They appear to enjoy the companionship of the baby, manifest some degree of

*Note.—The regulations of the Board of Health of the State of Pennsylvania require that 2½ to 3 hours of nursing care be provided for each baby per 24 hours, or about one nurse to every 7 or 8 babies. The same regulations require that each mother be provided with 4 hours daily of nursing care, or one nurse to every six patients. Upon a frank review of our situation during wartime and in the subsequent period of nursing shortage, we found we were providing an average of about one hour for each baby per day, and about two hours for each mother per day. With the inauguration of 8-hour general duty nursing, these hours have not much changed to the present.

from its mother, and whatever the psychic effect of this separation might ultimately be on mother and child, we were certain that we were destroying a natural and very normal relationship between the mother and her offspring.

Results

It would be unwise to draw conclusions categorically on the basis of this brief nine months' experience. However, there are certain results that have impressed us as having possible significance. First as regards the health of the newborn.

In the 1,018 full-term babies housed with the mother, there have been no cases of diarrhea or impetigo and only one case of mild (questionable) respiratory infection. In the latter instance, the baby was isolated for two days because the mother had a fever following the delivery and the nurses thought the baby had a beginning upper respiratory infection. Examination by the pediatrician failed to confirm this diagnosis and the baby developed no further symptoms.

We are quite conscious of the fact that this fortunate state of affairs will not continue indefinitely and that sometime a baby in one of these wards will develop diarrhea, impetigo, or respiratory infection. If such a thing occurs, however, we know that we can immediately isolate the affected baby, that the other five babies of the ward room will have been only distantly exposed, and that the ward room can be closed to further admissions until all contained mothers and babies are discharged and the space is cleansed. This should offer quite a favorable contrast to the old arrangement in which thirty or more babies in a nursery are exposed to the infection of any one of them.

There have been no really disturbing reactions in the baby at the bedside of the mother. Occasionally a baby will choke with milk after breast or bottle feeding. As she has been instructed, the mother turns the baby on the side, pats its back, and calls the nurse. We are of the impression that the mother detects these disturbances much earlier in the baby at her bedside than do the nurses in a large nursery.

In addition to these considerations which have to do with the health and safety of the newborn, we have noted that these babies, lodged at the bed-sides of their mothers, seem to be happier and more contented (if happiness and contentment can be assayed at such an early age) than they were in the nurseries. If a baby starts to cry, the mother reaches over and pats it, inspects its diaper to see if it needs changing, and nurses it if it is hungry. All attending obstetricians, nurses, and visitors are surprised at the quietness of the wards. There is nothing that even remotely approaches the pandemonium of a nursery during the late interval of a third or fourth hour feeding schedule.

Our second major consideration was as to how the rooming-in plan would affect our preconceived ideas of nursery care and distribution of nursing time. The observations on this score are of particular interest and possibly of considerable importance. Once we had the necessary equipment for individual treatment, the change from nursery to bedside care was made without a particle of difficulty. Thus far we have made no change in the traditional assignment of nursing activities—labor and delivery room, nursery, floor duty, formula room, out-patient department. The girls on nursery duty still have charge primarily of all babies: those in the premature nursery, the few in the central full-term nursery, and the babies at the mother's bedside. It is they who make the ward rounds in the morning and check the babies periodically during the day. The nurses on general floor duty during the day and night, however, are instructed to help with the incidental problems that occur in the mother and baby during the interim, and in this respect the lines of duty are not drawn as rigidly as before.

epidemics among the newborn. The care of the baby has also been simplified and there has been no addition of nursing hours.

The babies have seemed to be contented and happy under this arrangement, have gained rapidly in weight, and the percentage of breast feeding has increased.

The mothers have in general enjoyed having their babies with them. They have learned to take care of the baby from the first postpartum day on and have left the hospital quite capable of managing the ordinary problems of infant care.

The arrangement of housing baby with mother has been found to depend for its success to some degree upon early ambulation and breast feeding, and, in turn, the housing-in arrangement aids in involution and encourages breast feeding.

The plan also seems to work particularly well in small wards where mothers can watch each other, teach each other, and can be under the frequent observation of the nursing personnel.

The question of how well this plan will work in the private and small semi-private rooms has not been adequately answered. However, we see no reasons why the plan will not work there, too, if the proper modifications and adjustments are made.

2031 LOCUST STREET.

Discussion

DR. GEORGE W. KOSMAK, New York City.—We have been favored at this meeting, as at all previous meetings, with a large number of eminent scientific papers. However, it seems to me that we should not neglect other phases of obstetric care and particularly such topics as that which has been so admirably discussed by Dr. Montgomery. Now in the past with more confinements in homes, it was nothing unusual to have the baby with the mother and yet when the incidence of hospital deliveries increased these elaborate methods of care kept growing which in the course of time have been demonstrated to have certain disadvantages enumerated by the speaker. It is a matter of regret that the subject has been approached so much from the negative rather than the positive side. Dr. Montgomery has carefully outlined how the new system has cut down the nursing time and has made other improvements, but it seems to me that they should be balanced with the more satisfactory relationship between the mother and the newborn baby. These babies are kept in the nursery during their hospital stay and often the mother does not see the baby unless she is nursing him, until time for discharge, whereas it is that time which should be given to the mother to become accustomed to the baby and to know what are his needs.

Another thing, many of these women get a sort of demonstration the day they leave the hospital and a lot of information is put in this short period which is necessary to be remembered by the mother. It was very satisfactory to have Dr. Montgomery state that breast feeding has been encouraged by this method because I think it is one of the great failures of our modern hospital system in the care of babies, that not sufficient breast feeding is being encouraged. I believe that is one of the most important things to be considered in connection with this new scheme. It requires very little alteration in the hospital facilities. My own experience is very limited but I have found a lack of cooperation, unfortunately, between the nurses and the patients and the doctors in attendance, and that should be eliminated.

Many women come to the hospital, after having gone through perhaps a distressing period of pregnancy, with the idea that they want a good rest. However, as Dr. Montgomery has stated, it is not really a big chore for the mother to take care of the baby's requirements. It would be very fortunate indeed, I believe, if more institutions throughout the country could develop this rooming-in system so that we could have a further trial of it.

pleasure and pride in its proper care, and are jealous of its interests and safety. They do not want other patients to handle their babies and they make certain that no one comes in the room without a gown. All of them learn more about the care of their babies and are in better position to take care of their own babies upon discharge than they have ever been before.

Among the semiprivate patients, the young first mothers are the quickest to realize the value of the new project to them and are the most enthusiastic. Having been up and about at an early date following delivery and having taken care of their babies in the hospital, they have no qualms about their ability to care for the newborn when they go home. This is quite a contrast to the attitude of our primigravidae patients of a short time back.

Many of the multiparas state that they are sorry that they could not have had all of their babies this way. Others, who have lost some of the enthusiasm of their early pregnancies, look upon the arrangement as an imposition. They are frank to state that they have come to the hospital to get a rest from their household duties and care of children, and the plan is little to their liking. However, even in this latter group, if the baby is moved back to the central nursery, the mother says she misses him and is greatly concerned to know how he is doing.

The factor of knowing what is going on with her baby may be one of the important considerations for the mother in the rooming-in of babies, for the instinct of motherhood is still strong in the grand multipara as well as in the primigravida. With the baby at the bedside, no longer does the mother lie awake at night wondering whose baby is crying in the nursery, what the pediatrician thinks of the progress of her child, or whether any information concerning her offspring is being withheld. Now she has the situation entirely before her. If her baby cries, she will find out why with no delay. If she has questions for the pediatrician, she can ask them while he is examining the baby in her presence. She will know all the reactions and characteristics of her baby before she bundles him up and starts for home.

Perhaps it is not superfluous to state that the rooming-in of the babies has not interfered in any respect with the work of the obstetrician. As a matter of fact, with the two patients together it gives him a more complete picture of the mother-baby relationship and puerperal progress. He makes his rounds as usual and attends the antepartum and intrapartum patients as before. The pediatricians are more than pleased with the progress of these babies, the absence of infection, the excellent care of the newborn and the apparent contentment of the newborn, and the high percentage of breast feeding.

Just how successful the arrangement of rooming-in of babies will prove in the case of private and semiprivate patients in our hospital remains to be seen. A few patients who have desired their babies with them have been granted the privilege, although the special equipment used in the wards was not available. These mothers have expressed the same satisfaction and pleasure over the arrangement as the patients in the wards.

Feeling that the procedure is sound, we are securing the few essential articles of equipment that are necessary to make this arrangement also accessible to the occupants of private and semiprivate rooms. We foresee problems and difficulties but believe that these can be surmounted.

Summary

A system of baby care by the mother, in which some 1,018 babies, ward and semiprivate, have been housed with the mother, has been presented.

This system has satisfied the requirements for which it was set up, i.e., there have been no ill babies among these housed-in babies, and there have been no

Many European hospitals are now using and have for many years employed "rooming-in" baby care. Rooming-in is an interesting experiment which is well worth further trial and study in this country.

Maloney quotes a Taoist inscription which says in part, "... he who knows how to cleanse the current of a stream begins by cleaning out the source. And he who would straighten the end of a process, must commence by making its beginnings correct."

DR. HARVEY B. MATTHEWS, Brooklyn, N. Y.—The one point I would like to make is that if an institution such as the Rotunda, which has not closed its front doors for 203 years, has used the housing-in method with entire satisfaction, it is certainly worthy of trial by us American obstetricians, particularly under present-day conditions. I think, furthermore, we have allowed ourselves to foster the establishment of central nurseries with too many frills and foibles and that we should come "back to earth" and pay attention to what Dr. Montgomery has outlined.

DR. EDWARD L. KING, New Orleans, La.—Just a word to substantiate what Dr. Matthews has said. I have noticed that same situation in Dublin in the Rotunda and also in the Coombe Hospital. At the latter, it is carried to the full extreme and the baby stays in the bed with the mother the whole time. One of the Dublin pediatricians addressed the Conference and he said that in their three hospitals the percentage of trouble in the way of infection and diarrhea in the baby was less in the Coombe Hospital where the baby was kept in the bed with the mother. Next was the Rotunda Hospital where the baby was in a separate crib, and more trouble was found at the National Maternity where the hospital and nursing were more modern. In London, at the Queen Charlotte Hospital, they had much the same system; and in two hospitals in Paris they seemed not to have heard of a central nursery but have always had the babies with the mothers.

DR. MONTGOMERY (Closing).—Apparently the discussers, all of them, agree that there is a very salutary trend in this rooming-in project of baby with mother toward the simplification of baby care and that the more this care of the newborn is simplified and brought back under the mother's observation, the better are the results, both immediate and remote.

I would particularly like to emphasize the fact that this project requires no special or unusual architectural adjustment in the hospital maternity. Our own institution was never planned for such a project. In fact, the maternity division was built at a time in which the central nursery was considered to be quite the thing. Actually, it has cost us about \$6 a crib to provide the equipment for each baby. And I think this equipment has proved just as satisfactory and perhaps more so than some of the very complicated apparatuses which I have seen for the individual care of babies in a room or in a central nursery.

I would like to emphasize the fact that these babies are getting much better care and more constant observation with the same amount, or perhaps less, of graduate nursing than before, and that we are able to use this graduate nursing to great advantage in the premature nursery and in the care of the ill baby or ill mother. With the shortage of undergraduate and graduate nurses, this is an important consideration with us and I imagine it is going to prove an important consideration elsewhere.

I have the feeling that this project is going to develop and spread throughout the country and that, as soon as the advantages, both physical and mental, to mother and baby are realized, there will be a growing demand by mothers to have their babies with them throughout the hospital puerperium.

DR. ROBERT D. MUSSEY, Rochester, Minn.—Early ambulation of the woman following delivery and housing the baby with the mother are two innovations in the generally accepted routine of postpartum care.

The authors are conservative in not drawing definite conclusions following the comparatively short trial period, although they state that they are sufficiently convinced of the value of the program to justify its further trial.

Somewhat over a year ago, Dr. Anderson Aldrich, Director of the Child Health Institute in Rochester, Minnesota, discussed "rooming-in" of the baby with the mother with the Staff of the Obstetric Department and with those in charge of nursing and administration at St. Mary's Hospital, in the hope that it would lead to a trial of this procedure in the care of the newborn in the above-mentioned hospital. Up to the present, its trial has been delayed, owing chiefly to problems of nursing and architectural arrangements.

I was interested to attend an open discussion of this subject, under the chairmanship of Dr. John Parks, at the last Congress on Obstetrics and Gynecology at St. Louis. Since then, and particularly after being asked to discuss this paper, I have become more familiar with the pros and cons of "rooming-in."

More or less haphazard neonatal care forty and fifty years ago gradually has been replaced, chiefly owing to guidance by the pediatrician, by the set regimen of baby care which still obtains. Employment of a central nursery for all well babies except those born prematurely, strictly regulated hours of breast nursing at which time the baby is carried to the mother for breast or bottle nursing has obtained on the average obstetric service; too frequently bottle feeding is done in the nursery. Under this regimen the baby is separated from the mother except for brief nursing periods amounting in over-all time to approximately one and one-half hours daily. When the baby cries, if the nursery service is adequate and alert, he is given individual attention and then must wait completion of the routine three- or four-hour interval for the next nursing period.

The newborn baby, which, during gestation is enveloped by the mother, nourished and protected by her, is abruptly separated from her at birth. Instead of that close maternal association and protection which obtains in the case of practically all newborn warm-blooded animals, the human infant is placed in an environment of asepsis, technique, and rules, removed from maternal contact and protection, except for more or less widely spaced periods of feeding.

Proponents of the central nursery system have argued that this system is more practical from the standpoint of nursing care and safe supervision of the baby, and that the routine nursing interval is of value in beginning to train the baby in regular habits.

A few years ago, Aldrich and his associates carried out for a month twenty-four-hour observation periods in the nursery during which the crying time of each baby and the apparent cause of crying were charted. It was found that the total time of crying was almost inversely proportionate to the individual attention it was possible for the nurses to give the baby. Aldrich stated that during the early weeks of life a tabulation indicated also that nursing infants select a periodic time for nursing routine, if permitted to do so. This permits a nursing schedule to be established to the individual needs of each infant.

Those who favor rooming-in present many arguments in its behalf. Time does not permit repeating all of these. The author has emphasized the danger of infectious diarrhea of the newborn as compelling evidence against the large central nursery.

Also, the proponents of rooming-in state that it assists the mother, under proper guidance, to develop her responsibility in caring for her baby, that it gives a psychological lift to both individuals in the mother-infant relationship and a return to an approximation of the relationship which obtained before the advent of the modern nursery for the newborn; it permits well-mothered infants to develop into more psychologically stable adults, and even enables the father to evaluate better his role in the infant-parent relationship and to adjust himself to it.

used, and in all three "menstruation was easy since the operation, though the os was smaller in each than natural, and required to be enlarged by slight incisions." He concluded, "So in amputating the cervix, it is not necessary to cut it off even with the vaginal insertion to insure a good result, for whatever is left will be decreased by a modified nutrition, just as we see after amputation of the arm or leg."

Thomas Addis Emmet³ was the first to emphasize clearly the importance of laceration as the underlying cause of eversion, erosion, and chronic cervicitis. He devised a plastic operation in which the lateral portions of the affected surfaces were freely denuded, leaving in the center of each lip an undenuded strip which formed the continuation of the uterine canal to the external os. By 1874 he had performed this trachelorrhaphy operation nearly two hundred times, with ultimate benefit in most cases. In discussing Emmet's paper, Sims stated, "I have performed the operation often enough to speak in positive terms of its value. The discussion of the subject must of necessity be one-sided. There can be no objection, no opposition to the operation. We must accept it as Dr. Emmet has given it to us. We can't modify the operation; we can't change it; we can't improve it; it is perfect: perfect in method and perfect in its results. We owe Dr. Emmet a debt of gratitude for this valuable contribution to gynecologic surgery." Incidentally, this and other free exchanges of credit indicate the unselfishness and high character of these two great pioneers in gynecology. In regard to this particular operation, however, the results of leaving part of the diseased tissue as the central undenuded strip became evident under later critical observation and analysis of results.

In order to secure the benefit of complete excision of diseased tissue and yet avoid the difficulties following regular amputation, various modifications of amputation were made by a number of workers, including Schröder,⁴ Bonney,⁵ and Kelly.⁶ In 1913, Leonard⁷ made an excellent statistical analysis of the postoperative results in cases of amputation of the cervix done in the preceding twenty years in the Gynecological Clinic of the Johns Hopkins Hospital. There were four hundred cases but he was able to obtain complete protocols in only 128. He states, "The results were quite unexpected and in many ways disappointing." In regard to postoperative bleeding, he found that the dangers from serious hemorrhage after amputation were very real. Many of the cases required tight packing and five per cent of the cases bled so profusely at some time during the convalescence as to require removal to the operating room for resuture of the cervix.

In an article the following year, Leonard⁸ compared the results of amputation with those of trachelorrhaphy. In his series of trachelorrhaphy cases there was no serious bleeding and only six cases required a light pack. In ten first-child deliveries after trachelorrhaphy, only one was difficult; whereas, in eleven deliveries after amputation, seven were difficult. But in regard to cure of the cervicitis with its leucorrhea, he found trachelorrhaphy undependable and concluded that "although trachelorrhaphy may render mild cervicitis more amenable to treatment, it cannot be considered a curative measure for this condition."

It was in 1916 that Sturmdorf⁹ devised a technique which would permit removal of all of the diseased tissue and yet not complicate future labors. The steps in this procedure were: 1. Outlining and free mobilization of an ample circular flap from the vaginal coat of the cervix; 2. Complete excision of the entire cervical mucosa to the internal os; 3. Sutural coaptation of the vaginal cuff to the denuded cervical cavity. After critical test of results over a period of three years, he found that the operation fulfilled the requirements for which

WIDE CONIZATION OF CERVIX*

Follow-Up of One Thousand Cases, Six Hundred From Two to Fourteen Years

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THE problem of the operative treatment of extensive chronic cervicitis has taxed the ingenuity of some of the outstanding leaders in gynecology since the early part of the nineteenth century. A brief review of the main steps in working out the solution of this problem will help one to realize the difficulties encountered, and will give an historical perspective of the development of our present-day methods.

Historical Notes

Lisfranc,¹ in 1815, was one of the first to attack the problem. In cases which he presumed to be early cancer, he removed a wedge-shaped block extending from the vaginal margin of the cervix up to the internal os. This wound was allowed to heal by granulation over a period of five to six weeks. These patients were usually treated in the hospital for four to six months before operation was attempted. Later investigation demonstrated that these cases were not cancer but chronic inflammation with induration and hypertrophy of the cervix.

In 1860, J. Marion Sims² credited Huguier, of Paris, with performing this operation oftener than any other surgeon, and states that he (Sims) and Emmet had used the method frequently; but Sims found that the prolonged period of granulation resulted in dense strictures which could not be relieved by repeated incisions or other methods of dilation.

In attempting to improve the operative treatment, Sims first tried splitting the cervix transversely nearly to the vagina and then amputating in such manner that a conical excavation with apex upward remained. The strictures were just as persistent with this type of operation, even when he did it in two stages, removing the anterior and posterior lips a month apart. He then revised the technique further, stating, "I removed five-eighths of an inch of the cervix, cutting at right angles and within half an inch of the vaginal insertion. On beginning the operation, I intended to leave the cut surface to heal by the granulating process, which usually takes five or six weeks, but while sponging the wound and waiting for the hemorrhage to cease, I discovered that the stump could be covered over with healthy vaginal tissue in the same manner that a stump of an arm or a leg is covered after amputation by the circular method. This was done by passing four sutures of silver wire through the anterior and posterior borders of the wound which, when tightly drawn, brought its edges into apposition in a straight line across the middle of the stump, covering it completely, but leaving a small central opening just over the outlet of the cervical canal." The sutures were removed in a week. He reported three cases in which this operation was

*Read, by invitation, at the seventy-first annual meeting of the American Gynecological Society, Williamsburg, Virginia, May 24 to 26, 1948.

a deficiency of thiamine and riboflavin, which control normal mature development—hence, the forced growth is toward embryonic cells and in certain patients toward malignant change. If this theory is substantiated, it will constitute another reason for prompt removal of chronic cervicitis.

Concerning the prevention of cervicitis, with its cyst formation and eversion and extensive inflammatory infiltration, the importance of primary repair of cervical tears has been stressed by Bubis,¹⁶ Emge,¹⁷ Polak,¹⁸ Farrar,¹⁹ and others.

As to office procedures in chronic cervicitis, linear cauterization with the nasal tip (Fig. 1), first advocated by Dickinson,²⁰ has long been accepted as an excellent method of curing mild erosion and eversion. A more recent addition to office procedures for these mild cases is the endocervical conization introduced by Hyams.²¹

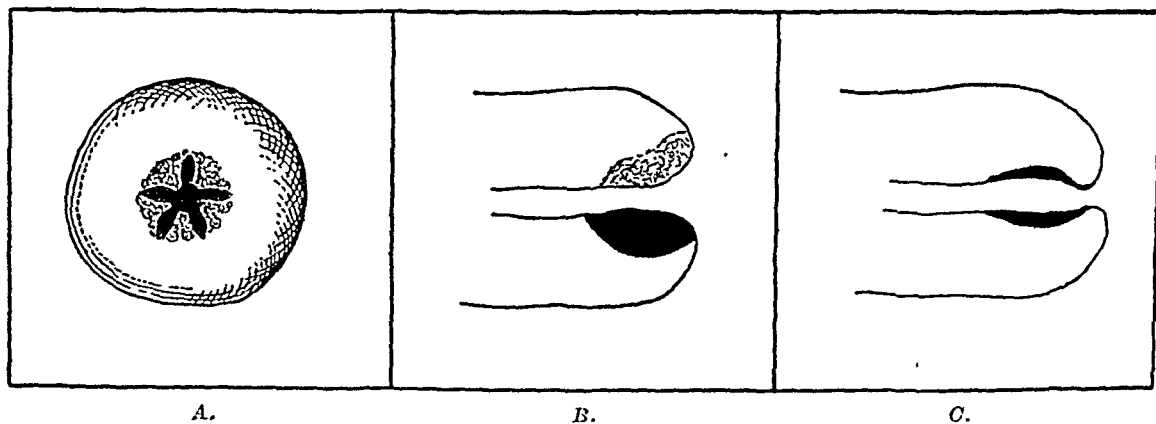


Fig. 1.—Linear cauterization of the cervix. A, showing the cautery incisions, and also the type of lesion suitable for this treatment; B, showing the deepening of the cautery incisions on the inside, so as to secure inversion from the scar contraction; C, indicating the satisfactory overcoming of the eversion, by the drawing-in effect of the inside scars.

Mortimer Hyams did a splendid service for the profession when he presented the principle of conization for endocervicitis. The presentation was made in 1928, and was followed by other papers giving his further experience with the method. The general arrangements for conization are shown in Fig. 2, and the shape and size of his electrode and its position in the cervix are shown in Fig. 3, both illustrations being from his paper. Hyams' object was to remove the endocervical mucosa. He shaped his electrode accordingly, and it accomplished the purpose admirably. He insisted that the removal of tissue should be limited to that within the canal and to the $\frac{1}{8}$ -inch width of his electrode.

Wide Conization

In the handling of chronic cervicitis cases, I became convinced that a wider excision would permit a cure of the extensive cases by conization. In a large proportion of the cases, the inflammatory process and cyst formation has extended beyond the endocervical mucosa out onto the vaginal surface of the damaged cervix and into the underlying deeper tissues. For removal of this widespread area of affected tissue, a larger electrode of different shape was needed, so I took up the problem.

Not being able to find the type of electrode needed, in a search of catalogues and in communication with various diathermy companies, I made sketches

it was designed; namely, it eliminated the diseased portion of the cervix, preserved the normal arrangement and contour and function of the cervical musculature, secured permanent accurate coaptation of flap to stump, and obviated the extensive scar tissue stenosis which had caused serious labor complications after amputation.

Harvey Matthews¹⁰ in an instructive analysis of two hundred cases of Sturmdorf operation, followed six months to three years, found 64 per cent were cured, 28 per cent were improved, and only 8 per cent were failures. He stated that, while the method was not a perfect one, it was the best so far devised for eradicating the infected area, and that it caused no more trouble with subsequent labors than did the required extensive trachelorrhaphy. In England, John W. Burns¹¹ analyzed the results of the Sturmdorf operation in ninety-two cases followed for two to three years. He found that only three cases remained uncured, and two of these had had gonorrhea. Of the ten full-term pregnancies, all had normal deliveries.

In spite of the various painstaking analyses showing the deficiency of trachelorrhaphy, this incomplete operation continued popular, presumably because the alternates (amputation and Sturmdorf) were more formidable and the smaller operation did effect satisfactory relief in many cases in which the inflammatory infiltration was largely lateral. In the discussion of a paper by Polak¹² in 1923, John G. Clark, Brooke M. Anspach, C. P. Noble, F. E. Keene, and Richard Norris still felt that trachelorrhaphy was preferable.

An excellent compilation of the results of trachelorrhaphy, amputation, and the Sturmdorf operation was made by Pendleton Tompkins¹³ in 1935. In addition to summarizing many series of reported cases, he gave the results of his study of 611 cases done at the University of Pennsylvania Hospital. From this comparison of the results of many operators, the statistics showed cures by trachelorrhaphy in 70 per cent, by Sturmdorf operation in 80 per cent, and by amputation in 83 per cent; but when the difficulties in labors subsequent to amputation are considered, the Sturmdorf procedure is decidedly the preferable operation of the three.

Deep coagulation by the high frequency current (and its predecessor, deep cauterization) have had quite a run of popularity alongside the other measures mentioned, and coagulation is still advocated by a considerable number in this country and abroad. However, it has some very undesirable features. W. T. Black,¹⁴ in a review of results of treatment of cervicitis, reached the conclusion that the dead, odoriferous slough which remains for some time after coagulation is followed by hemorrhage, by inflammatory complications including pelvic abscess, and by stenosis more frequently than is found after other cervix operations. A very serious objection to coagulation is that it precludes microscopic check of the removed tissue. This chronically irritated tissue may harbor beginning malignancy, and an important feature in the handling of chronic cervicitis is removal of the affected tissue in such a way as to permit microscopic investigation of every part of it. Removal of a specimen before coagulation is not sufficient, for the early carcinomatous cell change may be in another area.

It is not necessary to labor the point that chronic cervicitis is a factor in the causation of cancer. The voluminous literature on the subject has long since established that fact and shown the imperative need of prompt removal of this chronically irritated tissue—if possible before carcinomatous change develops, and most certainly in a way that will permit of thorough microscopic investigation. Incidentally, in connection with the long search for the relationship of cervicitis and other factors in the causation of cancer, it is interesting to note the theory recently presented by Ayre¹⁵; namely, that chronic irritation in the cervix causes a local excess of estrogen, which unduly stimulates growth, and

After devising the electrode and securing its manufacture in 1933, it was subjected to extensive clinical testing, not only by myself but also by other gynecologists. After its use in eighty cases by sixteen members of the Gynecological Staff of Washington University and Barnes Hospital, the new electrode was reported in 1935.²² As more experience was gained with the technique, we extended wide conization to cases which were still more extensive and in which we were still using the Sturmdorf operation, and found that this extremely wide coning by the electrode worked well.

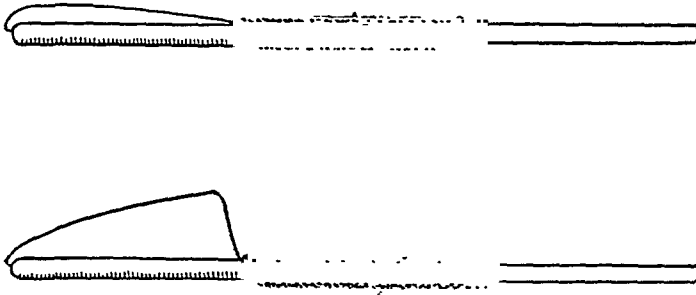
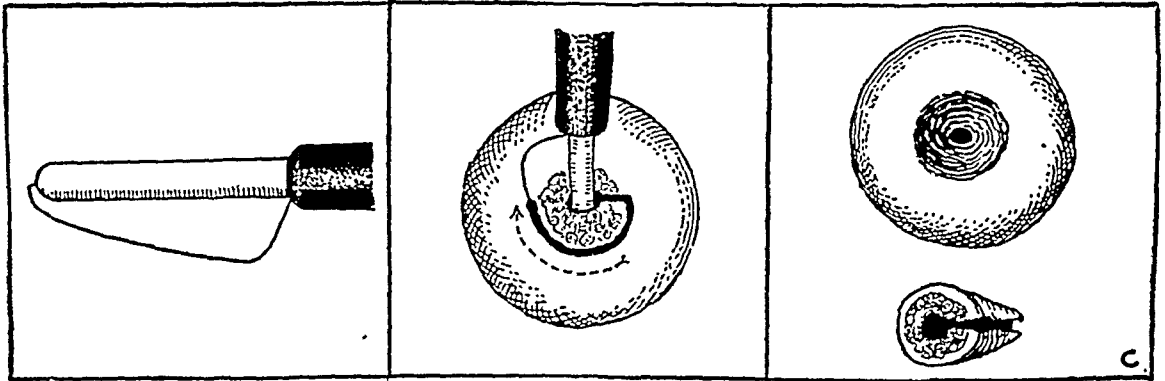


Fig. 4.—Upper electrode a Hyams, wire is one-eighth inch from the central core. Lower electrode is a medium-sized Crossen used for the wide conization to include all of diseased tissue. (Crossen—*Am. J. Obst & Gynec.*)



A.

B.

C.

Fig. 5.—A, The new electrode for wider conization.

B, Indicating the method of using the electrode, i.e., a wide excision taking in all the affected area.

C, The excised cone of tissue; also the remaining funnel-shaped cavity, which heals rapidly with good inversion. (R. J. Crossen—*J. Missouri M. A.*)

In the early work with this electrode, bleeders were coagulated with a ball electrode or with the wire, but it was found that these were the cases which gave trouble with delayed bleeding. We were reluctant to place sutures to control bleeding, for we did not know then whether the approximated coned surfaces would heal. However, by observing the occasional case in which bleeding necessitated suturing, we found that the healing progressed normally. For a considerable time suturing was limited to cases with active bleeding or to cases with associated radium treatment for myoma or dilatation and stem for dysmenorrhea (experience having shown that postoperative removal of a tube or

of several types desired for trial. The High Tension Company of New York offered to make up some according to the specifications on my sketches. After experimenting with different types, I found that the type shown in Figs. 4 and 5 best accomplished the work desired; namely, complete removal of the affected

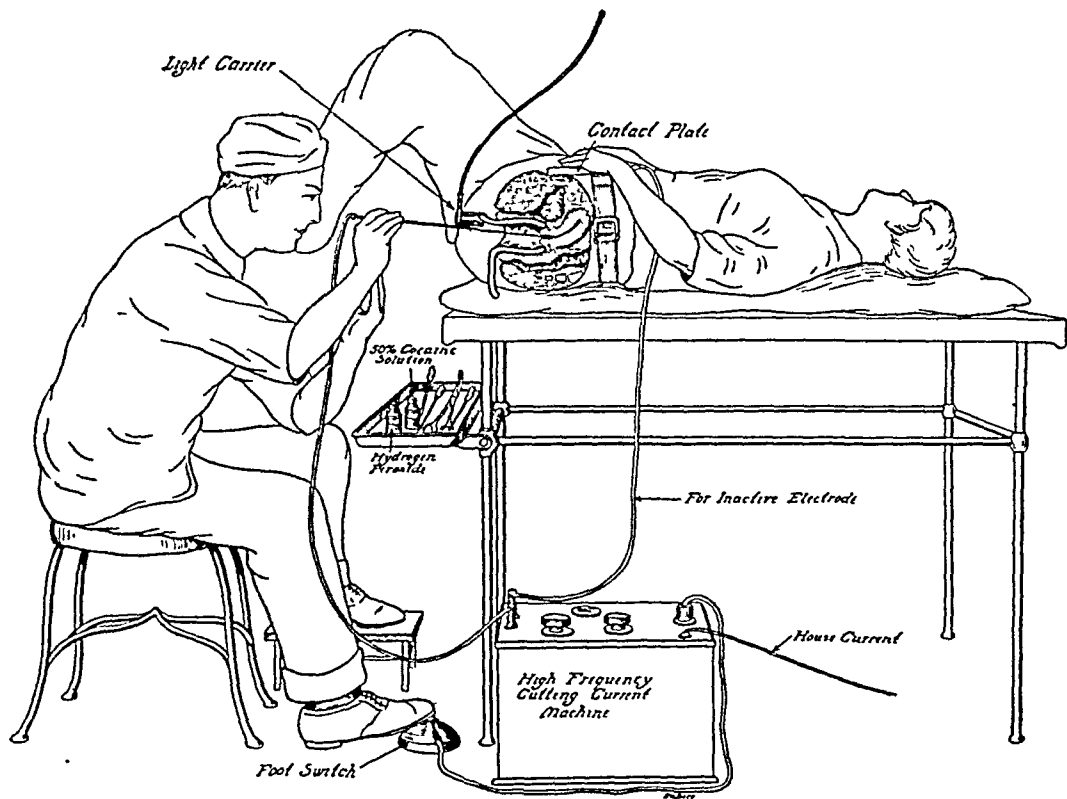


Fig. 2.—Schematic drawing of surgeon and patient during conization. (Hyams—*Am. J. Obst. & Gynec.*)

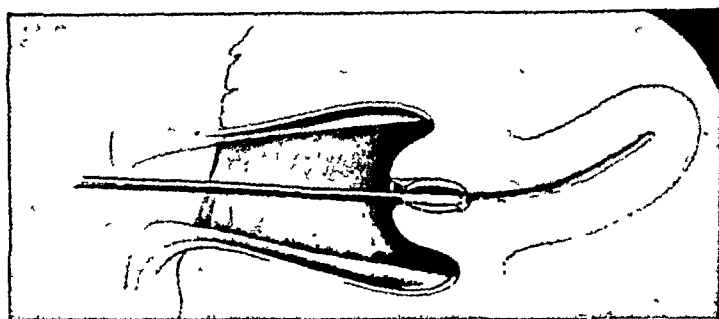


Fig. 3.—Hyams electrode in cervical canal. (Hyams—*Am. J. Obst. & Gynec.*)

tissue in extensive cases. I had in mind calling this a modified Hyams electrode, as it merely extended the application of the hemostatic-cutting current excision. But in his article Hyams had strenuously objected to having any electrode called a modification of his if it did not conform to his original specifications. Obviously, an electrode for this wide conization must depart radically from those specifications.

each side was left to form the new canal. Wide conization removes all the diseased tissue, and the turned-in flaps give an epithelial lining to the canal. Comparing it with the Sturmdorf operation, wide conization with the hemostatic-cutting wire does all that the admirable Sturmdorf operation did without the profuse bleeding and hurried hemostatic measures which were a normal part of the latter operation.

2. It removes all of the affected tissue in condition for microscopic examination. In this respect it has revolutionized specimen-taking from the cervix. Formerly, the custom was to remove a small specimen from the most suspicious area of the cervix, and if this did not show malignancy, to wait until another area began to look suspicious of malignancy and then remove a small specimen there—oblivious to the facts. (a) that there may be in any part of the affected area beginning carcinoma which does not yet look suspicious, and (b) that while the physician is waiting for suspicious signs, an early carcinoma may be making serious progress. Now, when chronic cervicitis is present, all of the affected tissue is removed by wide conization, and all is subjected to critical investigation in the laboratory. This settles at once and definitely whether or not there is beginning cancer.

Details of Handling Cases

Before going into the tabular analysis, I should like to describe briefly our usual way of handling these cases. For some time prior to the operation the patient uses an acid douche to improve the vaginal pH and flora. Before the war, when it was possible to select a time for the operation, the conization and curettage were scheduled for shortly after the menstrual period. The patient enters the hospital the day before operation, and a vaginal instillation of 1 per cent neutral acriflavine in glycerine is made as soon as convenient, and again the morning of operation, and again immediately after completion of the operation.

At operation, an electrode of suitable size is selected and the cervix is coned as shown in the illustrations. Occasionally it was found that a deeper cyst was opened but not removed in the first round, in which case the remaining area of affected tissue was removed by additional use of the cutting wire. However, it is well to avoid additional use of the cutting wire when practicable, by including all the affected area in the first round, the cutting wire being directed through healthy tissue with a good margin between it and the disease. Also, it is important to regulate the current so that it cuts as rapidly as is consistent with hemostasis, for slow cutting widens the narrow coagulation line and may damage an adjacent part of the specimen.

After the infected tissue is all removed, we place an anterior and posterior Sturmdorf suture to turn in the flaps. In doing so, we do not use the mattress-type bite in the lip as originally described by Sturmdorf, for in our experience the simple single bite, as shown in Fig. 7, turns in the squamous edge better than did the mattress type. In some of the early cases we tried undermining the vaginal mucosa, thinking to secure better coaptation of the flaps, but we soon discovered that the free bleeding nullified the advantage of the hemostasis obtained by the use of the cutting current; also, follow-up of the cases not undermined showed the ultimate result was excellent. One or

stem tended to loosen the small coagulation clots and favor bleeding). When the conization was exceptionally wide, a Sturmdorf suture, front and back, was used to draw in the flaps.

In 1939,²³ Dr. George J. L. Wulff and I reported three hundred cases of wide conization done by various members of the Washington University Staff. In that paper we reported also an improvement of the original electrode by Dr. T. K. Brown. He had the central metal core covered by an unbreakable lucite insulator instead of the very fragile one of porcelain previously used. Also, the nichrome wire was arranged so that it could be replaced easily and the loop size could be adjusted as desired for different electrodes. Fig. 6 shows the improved electrode and also the two sizes most frequently employed, the width of the larger being $\frac{5}{8}$ inch, and of the smaller, $\frac{3}{8}$ inch. The length of the cutting part is $1\frac{1}{4}$ inches.

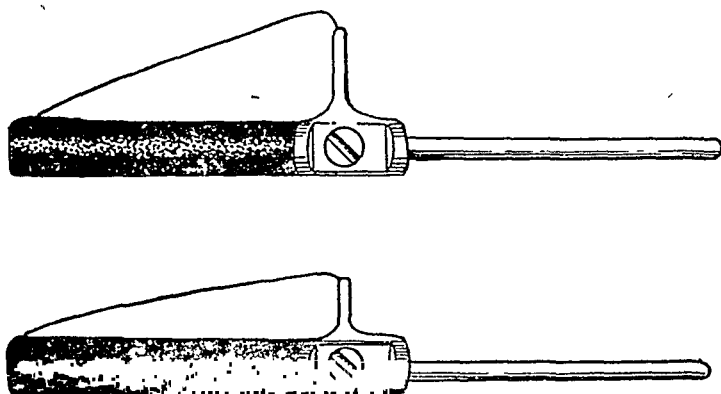


Fig. 6.—T. K. Brown modification of Crossen electrode. The unbreakable central core and replaceable cutting wire increase the durability of the electrode and reduce repair costs. (Crossen—*Am. J. Obst. & Gynec.*)

The method of relining the coned area is shown in Figs. 7 and 8—first a Sturmdorf suture front and back to draw in the flaps, then a superficial stitch or two on each side to turn in any everted edge, and then a tube in the canal to prevent healing across the canal and to guide epithelization. Though many cases will get along satisfactorily without the tube, we have come to use it routinely as a precaution. It should be of fairly small size so as not to make sufficient pressure to interfere with epithelization, and should have a T-piece on each end to prevent slipping down into the vagina or up into the uterine cavity, which has happened at times. Also, as with all pelvic or abdominal drainage tubes, it should be of red rubber, which is opaque to x-rays and, therefore, can be identified if lost in the uterus.

Wide conization was designed to accomplish and does accomplish certain important things for the patient:

1. It removes the extensive chronic cervicitis thoroughly, even though the process extends far out on the vaginal surface of the cervix and deeply into the tissues beneath. When there is associated old laceration with inflammatory swelling and eversion, there is produced the distorted infiltrated cervix for which trachelorrhaphy was formerly the accepted operative treatment. Trachelorrhaphy failed to remove all the diseased tissue, because a central strip on

anesthesia is needed to exclude silent ovarian carcinomatous infiltration. If the patient has a myoma with bleeding, the myoma activity can be stopped by a suitable dose of radium at the same time, and the curettage will exclude complicating endometrial carcinoma. All this is accomplished with a short hospitalization and anesthesia, and the patient goes home with the chronic cervicitis removed and with her mind free from anxiety as to something developing in uterus or ovaries.

The importance of taking advantage of the short anesthesia to do a curettage along with the conization is emphasized by the fact that this associated curettage revealed early endometrial carcinoma in eight of these patients. This point is still further emphasized by our experience in a series of myoma-radiation cases.²⁴ In the 549 myoma cases selected for radiation treatment, the preliminary curettage revealed endometrial carcinoma in 23 of these women. Incidentally, in this series of myoma-radiation cases, there were 233 conizations for chronic cervicitis along with the radium treatments for the myomas, giving abundant opportunity for observing the combination, and it worked well.

Since the introduction of wide conization in 1933 as previously described, and the published report in 1935, several series of cases have been reported by other gynecologists. Comparing certain features of the other reported series with the details of our present technique brings out some interesting points. In regard to control of bleeding, spot-coagulation is recommended by Norman Miller and Todd,²⁵ T. K. Brown,²⁶ J. J. Haber,²⁷ M. A. Roblee,²⁸ and M. L. Stadiem.²⁹ We started with spot-coagulation but our experience, previously detailed, caused us to adopt suturing, and we feel strongly that the routine suturing turns in the flaps better and gives more secure hemostasis without the small coagulation sloughs which favor secondary hemorrhage, particularly when a tube or stem is to be removed from the canal. The routine suturing, as shown in Figs. 7 and 8, has practically eliminated bleeding, and also hastens healing by accurately approximating the coned surfaces.

Routine postoperative dilatation when patient returns to office is advocated in most reported series. We felt at first that this was advisable, but with increasing experience decided that in many patients it was not needed, that the sound-test was often misleading as to a normal internal os, and that it was best to leave the internal os undisturbed unless there was evidence of trouble there.

In regard to the effect of conization on subsequent labors, Miller concludes that "In general, conization should be limited to women past the childbearing age." Roblee states, "Although we practice and teach that conization should not be performed during the active childbearing age, there is little clinical evidence in our hands to support this conclusion." Brown states that conization "will not interfere with subsequent pregnancies nor complicate future deliveries."

In our experience there was no evidence that conization caused trouble in subsequent labors.

Conization was frequently associated with other operative work. In the series, there were 267 associated radium treatments for myoma or delayed menopause, 119 abdominal operations, 116 vaginal plastic operations, and 32 com-

two superficial lateral sutures close any open area at the sides and then the tube is introduced. The small soft rubber tube with a T-piece on each end is placed with the upper end just within the internal os. This is removed just before the patient leaves the hospital, which is on the third or fourth postoperative day.

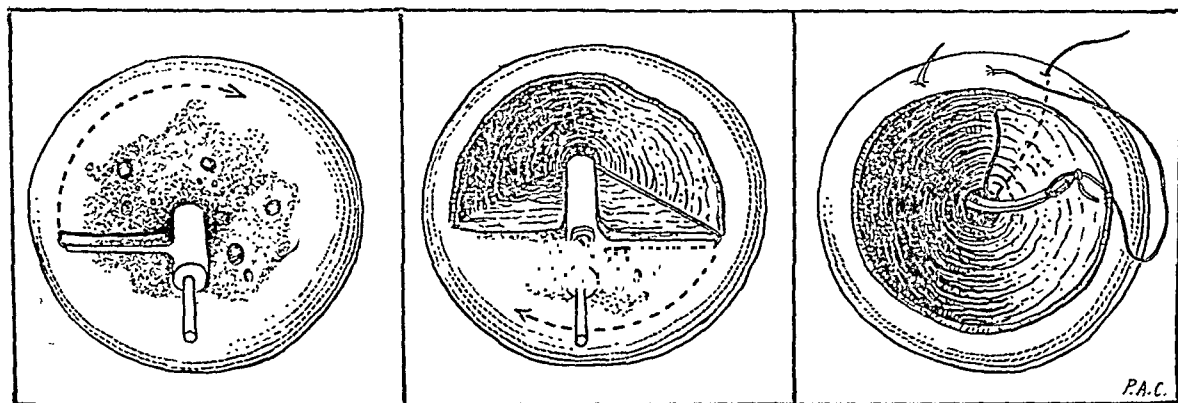


Fig. 7—Extensive conization with modified Crossen electrode, showing use of Sturmendorf suture on anterior and posterior lips to aid inversion during healing.

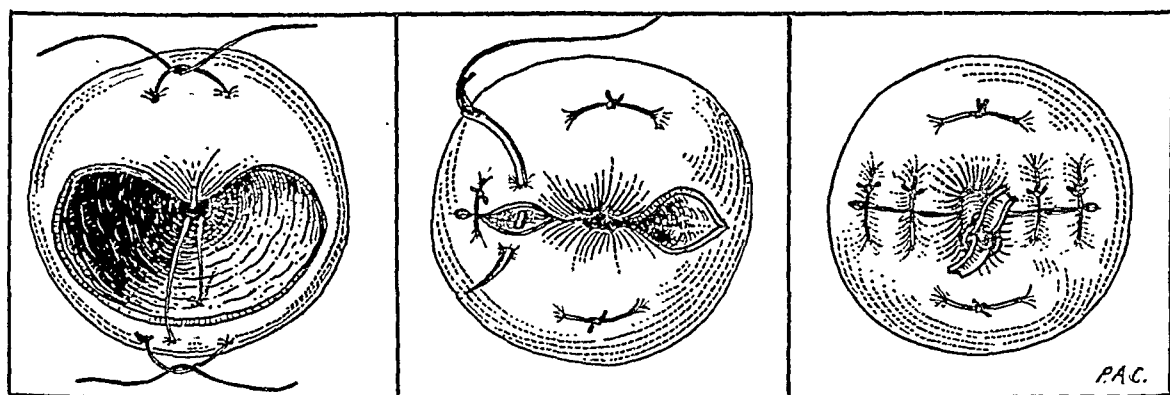


Fig. 8—Shows lateral sutures and completed procedure with the T tube in place.

On discharge from the hospital, the patient is instructed to take a daily lactic acid douche or vinegar douche. If there has been a definite vaginitis prior to the conization, an acid jelly or triple-sulfa jelly is advised in addition to the douche. When the patient returned to the office in four to six weeks, we formerly passed a small sound through the internal os to make sure there was no stricture, but we found that this was not a reliable test for stricture, for it is often difficult to pass a sound through the internal os of a normal cervix which has not been operated upon. At present we pass a sound only in cases where there seems to be some narrowing of the external os or cramping with periods or marked decrease in the menstrual flow.

Wide conization for extensive chronic cervicitis is a hospital procedure. Curettage also is needed in a large proportion of the cases as a therapeutic or diagnostic measure, and deep accurate palpation of the pelvic interior under the

satisfactorily and the ultimate results are as good as with the excellent Sturmdorf operation and without the free bleeding and hurried hemostatic measures which constitute a normal part of the latter operation. The items of particular interest in such a comparison are: postoperative bleeding, later stricture, conditions requiring additional treatment or reoperation, and effect on subsequent deliveries.

In this series of conizations, there were only eleven cases in which postoperative bleeding occurred, and in none of them was it severe in character. In one of the eleven cases the bleeding was not from the cervix but from the endometrium, and was stopped by curettage. In each of the other ten cases, the bleeding was controlled by a single tamponade.

There were 16 subsequent strictures in this series, the severity of the cases and required treatment being shown in Table II. Twelve of the strictures occurred within the first year after the conization, and the remainder within the first five-year period.

TABLE I. PERIODS OF OBSERVATION AND AGES OF PATIENTS

Less than one year	259	AGE GROUPING OF WIDE CONIZATIONS			
One year	112				
Two years	83	16 TO 39 YEARS		40 AND OVER	
Three years	74	NUMBER	PER CENT	NUMBER	PER CENT
Four years	70	436	43.4	569	56.6
Five years	44				
Six years	46				
Seven years	40				
Eight years	44				
Nine years	45				
Ten to fourteen years	188				
Total	1005				

TABLE II. STRICTURES, SHOWING TIME AFTER CONIZATION, AND TREATMENT

TREATMENT FOR RELIEF	NO.	TIME AFTER CONIZATION			DYSMEN- ORRHEA PREOP.
		UNDER 6 MO.	6 MO.- 1 YR.	2 YR.- 5 YR.	
Office treatment, dilatation, stem or tube	13	9	1	3	3
Operative treatment	3	1	1	1	2
Total	16	10	2	4	5

In Table III are shown details of the fourteen cases requiring reoperation under anesthesia. In three of these, the later operation was for stricture, and one also had complicating pyometra. In the other eleven cases, there was a reconization or excision of the cervical stump for cervicitis, which was either persistent from time of conization or a new development following labor or infection. In three of the eleven cases, the cervicitis had persisted because not all of it was removed in the primary conization. In the remaining eight cases, the patients had been well for five years or more, a fairly clear indication that the local inflammation was a new development. Three of these eight patients had intervening pregnancies, and one had been delivered three times since the conization.

In addition to the secondary treatment cases shown in the two preceding tables, there were 54 other patients for whom some minor treatment later was required to complete the cure. In 14 of these, the trouble was persistent from

bined abdominal and vaginal operations. We experienced no trouble from the combination of other operations with conization, except in an occasional case of radium treatment for myoma in which the radium extended to the internal os instead of being placed well above it. Particularly helpful is conization for any cervicitis in the cervical stump left while doing a hysterectomy which must be supravaginal instead of complete.

Analysis of Cases

The present study is an analysis of 1021 cases of wide conization for chronic cervicitis from the private practices of H. S. Crossen, R. J. Crossen, and George J. L. Wulff. The periods of observation are shown in Table I. We feel that the group is large enough and the cases have been followed long enough to permit drawing reliable conclusions as to the effectiveness of this method of treatment. The questions in our own minds which we sought to answer were:

1. Does wide conization with suture heal as well and give as good ultimate results as the Sturmdorf operation?
2. In how many cases did postoperative bleeding or later stricture occur?
3. Were subsequent deliveries complicated because of the conization?
4. In how many patients did the wide conization for cervicitis lead to an early discovery of cancer?
5. Did conization reduce the incidence of subsequent cervical cancer?

In the first place, the wide conization for chronic cervicitis and the associated curettage revealed early carcinoma in 16 of these patients (8 cervical, 8 endometrial), which, of course, removed them from the cervicitis class to treatment for cancer—leaving 1005 patients to be followed to determine the results of conization in cervicitis.

The follow-up of these patients was by examination in our office for 542, examination by other physicians for 105, and by questionnaire for 358. The questionnaire asking the following: (1) Have you had any troublesome discharge? (2) Have you had any later pelvic operation? When? What was done? (3) Have you had any pregnancies? Give number and outcome. (4) Have you had a pelvic examination since I last examined you? Was the pelvis found to be in good condition?

When a patient did not answer the questionnaire, her last office visit then constituted the end of her follow-up. Conization patients who did not have a checkup after leaving the hospital were not included in the series.

In order that our statistics could be completely unbiased, we asked Dr. A. C. Trueblood, who had nothing to do with the treatment of these cases, to obtain the information from the histories. We wish to take this opportunity to express our appreciation for his valuable contribution in carrying out this part of the work.

As seen in the figures on age grouping, nearly half of the patients were in the childbearing age.

Comparing this series of patients who had wide conization with reported series of the Sturmdorf operation and with our own work with the latter operation, we find that the conization wound made with the cutting current heals as

I have more experience with it than I have with a difficult forceps delivery, and this was important in my decision. I was anxious to get a living baby, and a man always tends to use the method he knows best." In my opinion, the cervix was not an important factor, if any, in this case.

The patient who had the difficult delivery from below had had four previous long, hard labors with difficult deliveries, due to the fact that the babies were all over ten pounds. With the first baby, the head had to be crushed to effect delivery. The postconization child weighed 10½ pounds and it was delivered by low forceps. Her obstetrician told me that there was no difficulty with the cervix, but because of the size of the child, the delivery was very difficult.

Of the 32 patients who did not carry to term, we had information on 29, and of these, 24 had abortions and 5 had miscarriages in the second trimester of pregnancy.

Of the abortion cases, there were three therapeutic, two induced, and three missed abortions. Five of the abortion cases were endocrine problems, one had had a preconization abortion, six had had at least one postconization full-term delivery. In four, no cause was evident, but all of these cases had well healed cervixes.

Of the five who miscarried, two had premature rupture of the membranes, one had lobar pneumonia, one had a serious automobile accident, and the last one had been doing an excessive amount of automobile riding.

Sterility has been mentioned as a possible result of conization. There are many causes of sterility, but we see no reason to think that conization, done with reasonably accurate technique, is one of them. In fact, it seems quite clear that conization puts the cervix in so much better condition in cases of cervicitis that it is a definite aid in overcoming sterility. One of our sterility-problem patients had four full-term deliveries after conization.

Wide conization for cervicitis led to the discovery of early uterine cancer in 16 patients. Eight of the 16 had early carcinoma of the cervix. This emphasizes the importance of removing the affected tissue in a condition for microscopic check of all of it. One of the cervix-cancer patients refused treatment and is dead. The other seven were alive without recurrence: two, 12 years; one, 11 years; one, 8 years; two, 4 years; and one, 2 years, after treatment. These findings emphasize the importance of eliminating this irritated battlefield of epithelia promptly instead of waiting for the first sign of cancer and then trying to catch up with it.

There were eight cases of carcinoma of the endometrium discovered at the time of conization by curettage, which is done *routinely* with conization. All eight were alive and well: two, 10 years; one, 8 years; one, 7 years; two, 4 years; and two, 1 year after treatment. Some men advise against curettage in conjunction with cervical operations, but these cases demonstrate the importance of doing it in every case.

In regard to prevention of cervix cancer by wide conization for chronic cervicitis, no cervix cancer occurred in the 1005 cervicitis cases during the periods of observation, and 407 of them were observed for five to fourteen years.

Summary and Conclusions

Brief historical notes sketch important steps in the efforts, from the early days of gynecology, to create an effective and simple operation for eradicating chronic cervicitis.

My study of the problem resulted in devising a special electrode and technique for making wide conization with the high-tension cutting current. After

the time of conization, and consisted of an everted lateral edge or some other minor defect in healing, requiring light touching with cautery. Our suturing technique of recent years, shown in Fig. 7, has almost stopped these edge eversions. Seven hundred twenty-seven cases received this suturing. The remaining 40 patients required late minor treatment for removal of polyp or puncture of a cyst or linear cauterization for a small area of erosion or eversion. We were able to check on all but eight of the questionnaire patients who answered "yes" on discharge. Those having cervicitis are included in the retreatment group, and the eight we were unable to check were counted as recurrent cervicitis.

TABLE III. REOPERATION CASES, WITH DETAILS

		NO.	1-2 YR.	2-5 YR.	6-12 YR.	
Reoperation for stricture	Plastic operation	2	1	1		(Dudley operation)
	Hysterectomy	1	1			(Also pyometra)
Reoperation for cervicitis	Reconization	10	1	2	7	
	Excision cervix	1			1	(Excision of cervical stump)
Total		14	3	3	8	

Counting the 14 cases reoperated upon and the 13 strictures requiring only office dilatation and the other 54 cases requiring some minor treatment to complete the cure and the 8 uncertain cases from the questionnaire, there were, in all, 89 cases requiring some later treatment—some for a condition persisting from the conization and some for a new development, such as polyp or cervicitis following labor or infection. In this group there were 48 cases in which our present suturing technique was not used, 36 in which no tube was placed at operation, and 11 in which a radium treatment was given in conjunction with the wide conization.

Taking up the matter of labor after conization, in our series there were 75 patients who conceived, having a total of 95 pregnancies. There were 63 deliveries at or near term, 49 of which were first deliveries following conization, details of which are shown in Table IV.

TABLE IV. FIRST DELIVERIES SUBSEQUENT TO CONIZATION

49 First, postconiza- tion deliveries at or near term	No difficulty	44	
	Difficult deliveries	4	Cesarean section. Ages 42, 39, 34, 38
		1	Difficult forceps delivery
			Two, because of previous difficult deliveries. One, head too large. One, several indications
			Four previous difficult deliveries, all over 10 lb. This one 10½ lb. Fractured clavicle due to size. No trouble with cervix.

The indications for the four cesarean sections were as follows: one elective section because of disproportion between pelvic inlet and size of fetal head; two were done because of previous long, hard labors terminated by difficult forceps deliveries. Both of these were sterilized, one had had two previous children and the other, who was 42 years of age, had had one previous child. The fourth patient who had a section was cared for by an out-of-town doctor. She was 38 years of age, had had two children and one abortion, and had her last child sixteen years previous to the section. With this labor she was two to four weeks postmature and she had a large child. After an eight-hour labor, with one-finger dilatation, a section was done and an eight pound, eleven ounce baby was delivered. The patient was sterilized by tubal ligation. The doctor stated, "I do cesarean sections quicker than you would in a large medical center, for

or near term. Forty-nine of these were first deliveries following the conization, as detailed in Table IV, and in none of them were we able to show evidence of trouble from the conization.

Our experience indicates that there is no substantial reason for denying the benefits of conization to women of childbearing age. In fact, we feel it is strongly advisable that they be relieved of the chronic discomfort of cervicitis and of the cancer menace it carries, and be thus put in better condition for future childbearing.

4. The importance of the outlined conization procedure in the diagnosis of early cancer of the uterus is shown by the fact that in this series wide conization for cervicitis led to the discovery of early carcinoma in 16 patients (8 cervical and 8 endometrial). Endometrial curettage is combined with wide conization routinely, as explained in the description of our technique. One of the cervix-cancer patients refused treatment and is dead. All the other 15 cancer patients were alive and well because the conization and accompanying curettage brought early discovery of the cancer and prompt treatment.

5. Wide conization for cervicitis definitely reduced the incidence of subsequent cervical carcinoma. None of the 1005 cervicitis patients developed cervical cancer during the periods of observation.

The estimated rate of uterine cancer in gynecologic patients generally is 4 per cent.³⁰ The ratio of cervix to corpus cancer varies much in different series, the average being about 5 to 1, or 80 per cent cervix,³¹ which gives a rate of 3.2 per cent for cervix cancer in gynecologic patients in general, and it certainly would be higher in a cervicitis group. Applying the rate of 3.2 per cent to the 1005 cervicitis patients, we find there would have developed 32 cervix cancers in the group. Considering the periods of observation and making generous allowance for possible developments after observation, we feel justified in claiming that the removal of the chronic cervicitis prevented cervix cancer in at least 25 of these women.

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devising the electrode and securing its manufacture in 1933, it was subjected to extensive testing, not only by myself but by several other members of the Gynecological Staff of Washington University and Barnes Hospital, and a report of this work with a description of the new electrode was published in 1935, and a further report covering additional cases was made in 1939.

In this 1948 paper there is presented a detailed analysis of a series of 1021 cases of wide conization for cervicitis, 634 of which were followed for two to fourteen years. This analysis of our experiences gives a basis for definite answers to the five questions which prompted the study. These questions will be answered here in the order in which they are given at the beginning of the tabular analysis:

1. Wide conization with suturing heals as well and gives as good ultimate results as the excellent Sturmdorf operation, and without the profuse bleeding and troublesome hemostatic measures which constitute a regular feature of the Sturmdorf procedure.

2. Postoperative bleeding was not troublesome, owing to the hemostatic effect of the high-tension cutting wire. In the eleven cases in which there was some postoperative bleeding, in one it was not from the cervix but from the endometrium and was stopped by curettage. In each of the other ten cases, it was controlled by a single tamponade. The use of routine suturing, as shown in Figs. 7 and 8, has practically eliminated bleeding. In the series, 727 cases were sutured, the unsutured or partially sutured ones dating largely from the earlier and experimental years.

Stricture occurred in only sixteen of the 1005 cervicitis cases during the periods of observation. Most strictures can be handled by office dilatation, only three of the sixteen in our series requiring retreatment in the hospital, as shown in Table II. Concerning routine postoperative dilatation as prophylactic for stricture, we have concluded that it is better to leave the internal os undisturbed except when there is evidence of trouble there. The reasons for this conclusion have already been detailed.

The other additional treatments required for persistent or recurrent cervicitis or for polyp or cyst or other minor condition have already been considered in detail in the analysis and tables.

As to the percentage of cures from the primary conization in the 1005 patients followed for cervicitis, there were 14 who required reoperation (Table III), 67 who required some additional minor treatment to effect a cure, and eight from the questionnaire who still had some undescribed discharge and presumably needed some additional treatment—giving 14 failures and 75 improved. Subtracting the 89 from 1005 gives 916 (91 per cent) cures by the primary conization. Additional cures were obtained by the secondary treatments.

Wide conization for cervicitis combines well with other operations, both vaginal and abdominal. In those cases in which a hysterectomy must be supravaginal instead of complete, conization is particularly helpful in eliminating the menace of continuing cervicitis in the cervical stump.

3. As to the question of conization causing difficulty with subsequent labor, in this series of 1005 conized patients, there were 63 subsequent deliveries at

Dr. Crossen has presented a commendable and careful analysis of his end results and they speak for themselves.

DR. HARVEY B. MATTHEWS, Brooklyn, N. Y.—As has been stated, there are a multiplicity of methods for the treatment of chronic cervicitis. No one is ideal but some are superior to others largely because the operator using his favorite procedure is more proficient in its execution.

I wish to present the following classification of chronic infections of the cervix, which we believe is of great help in choosing the best method of treatment:

Group 1. The recently lacerated cervix (of three to twelve weeks' duration) with superficial infection; or the nulliparous cervix, the seat of mild gonorrheal or nonspecific infection with or without slight erosion and no cyst formation.

Group 2. The lacerated, eroded cervix of from three to twelve months' duration with somewhat more extensive and deeper infection than in Group 1 and perhaps a few superficial cysts. This may obtain in a moderately deeply infected nulliparous cervix.

Group 3. The lacerated, eroded, everted cervix of two to five or more years' duration, moderately deeply infected and hypertrophied usually with visible cysts. A similar condition is present in the deeply infected nulliparous cervix with or without erosion and cyst formation.

Group 4. The neglected lacerated, everted, eroded, hypertrophied, cystic cervix, deeply and extensively infected and of long duration (fifteen to forty years). Rarely the nulliparous cervix may be similarly deeply and extensively involved.

This classification is simple and gives a thumb nail picture of the extent of the gross pathology present. It, furthermore, affords a convenient way of applying the various methods of treatment for each group. For example, we use the small nasal type of cautery for Groups 1 and 2 and for a few cases in Group 3. Conization is an excellent procedure for Group 2 and many cases in Group 3. Lately we have been using it more frequently than formerly because we feel it has advantages over the cautery for the deeper seated chronic infections. For Group 4 we invariably employ the Sturmdorf operation.

We do not believe, however, that wide conization without suturing is entirely safe. Permanent hemostasis is uncertain and stenosis of some degree is frequent and, in some cases, of such a degree as to require hospitalization for treatment. We have had very little experience with wide conization followed by suturing as described by Dr. Crossen. Certainly his results are excellent—91.4 per cent cured. However, there were 89 cases that required some form of later treatment because of wide conization. Sixteen of these were real strictures of the cervical canal and ten cases had postoperative bleeding that called for treatment. No bleeding case, however, was of a serious nature.

We cannot agree that this procedure requires less time, is easier to perform, and is preferable to the Sturmdorf operation. We still prefer the latter operation because, in our hands, it has all the advantages of conization with suturing and few, if any, of its disadvantages. Under ordinary circumstances it takes no longer to perform; hemostasis is certain; the biopsy specimen is just as adequate for microscopic study; stenosis of the canal should almost never occur (we have had one case in twenty-five years' experience); and the incidence of complications during pregnancy and labor is not appreciably increased.

In conclusion, it cannot be denied that one of the most important claims for conization (any type), but particularly with the wide type, is that it always furnishes an excellent biopsy specimen for microscopic examination. It, furthermore, provides excellent therapy in experienced hands and is frequently superior to cauterization of any type. We do not, however, agree, at least at the present time, that wide conization with suturing is preferable to the Sturmdorf operation which has, in our hands, all the advantages and very few, if any, of the disadvantages of wide conization with suturing.

DR. JOE V. MEIGS, Boston, Mass.—I have always felt that cauterization of the cervix, other than light cauterization of the cervix following delivery, had very little place

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Discussion

DR. WALTER T. DANNREUTHER, New York City.—At the time when conization of the cervix with the high tension electric spark was originated by Hyams in 1926, Sturmdorf's tracheloplastic operation enjoyed considerable popularity as a means of removing infected and diseased endocervical glands. The objectives of the two procedures were quite similar, and neither was intended to supplant light cauterization with a fine wire tip for simple ectropion; nor removal of the cervix for an extensively scarred, bulky, and cystic portio. The main purpose of both tracheloplasty and conization was to remove all of the infected endocervical glands with minimum damage to, or sacrifice of, the adjacent tissue, and they were never intended for lesions on the portio. The chief disadvantages of the Sturmdorf operation were the necessity for prolonged hospitalization and anesthesia, and the demonstration by Wolfe of Brooklyn in some 200 cases that, in many, islands of infected glands near the internal os escaped excision by the operation. Using the original electrode designed by Hyams, a high tension cutting current, a fifty per cent cocaine solution for local anesthesia, and correct technique, conization can be done as an office and clinic procedure, and the extent of tissue removal is easily within the control of the operator.

It would be difficult to compile statistics from the huge number of cases in which conization in both private and clinic patients has been done by the members of the gynecological staff at the New York Post-Graduate Hospital alone during the past twenty-two years, but I can say that we have never had occasion to modify the original equipment or technique in the slightest degree. In properly selected cases, subsequent serious bleeding, persistence of leucorrhea, cervical stenosis, and dystocia at the time of labor have never been a problem.

The Hyams electrode conforms to the anatomic fusiform contour and length of the cervical canal, and usually excises the endocervix to the depth of one-eighth of an inch. The high frequency machine must generate a fine, high tension, smooth, cutting current with a minimum of coagulation.

I feel somewhat handicapped in discussing Dr. Crossen's presentation because he is evidently now utilizing the desirable features of conization as part of a procedure which provides for a much wider removal of tissue on the surface of the portio and includes many of the features of a surgical tracheloplasty plus the use of a drain and even radium in some cases, and I have had no experience with it. For mere erosion alone surrounding the external os, or complicating chronic infections of the endocervical canal, we have not found a wide excision in this area necessary, as the subsequent contraction and retraction following the use of the Hyams' electrode have been adequate. What Dr. Crossen has done is to combine the principles of conization and Sturmdorf's sutures in a way which enables him to deal satisfactorily with practically all cases of endocervicitis regardless of the extent of the involvement of tissue. I thoroughly agree with his objection to the use of coagulation, but still feel that the fine wire cautery tip, total removal of the cervix, and hysterectomy have their place in some cases. It seems that Dr. Crossen's composite operation is a competitor with Sturmdorf's tracheloplasty for an extensively pathologic cervix, rather than a substitute for the original conization technique.

possibility of future childbearing. The other half of the patients in this reported series were past 40 years of age and the involuting uterus and ovaries in such patients do have a certain cancer potential. This latter group can be further subdivided into those in whom the chronic cervicitis was the only lesion demanding treatment, and those who had some additional condition needing treatment, such as a myoma. In this last group, I agree with Dr. Meigs that hysterectomy and bilateral salpingo-oophorectomy is the procedure of choice in patients who are good operative risks. In the group with no complicating condition, this extensive abdominal operation seems to me a very drastic treatment for a small but important lesion which, as has been shown, can easily be cured by a comparatively simple procedure which gives excellent results in a very high percentage of the cases. I am sure that had I advised hysterectomy in every case needing wide conization many would have had nothing done.

Dr. Dannreuther mentioned the excellent results obtained by the use of the Hyams electrode. As mentioned in the paper, we found this electrode excellent for use on the less extensive cases and we used it as an office procedure, but for the type of case under discussion it was entirely inadequate.

Dr. Baer states that most cases of cervicitis can be handled by deep cautery. Extensive deep cautery, such as would be needed in extensive, deep cervicitis, has the same disadvantages as coagulation, namely the tissue is not preserved for complete microscopic examination, and healing is delayed by the sloughing tissue. He says that the Sturmdorf operation need not be a bloody one if lateral sutures are placed before the conical excision. We formerly did the Sturmdorf operation and the lateral and circular sutures did help to reduce the amount of bleeding but it was still considerably greater than we get with wide conization. One must use any new procedure and get used to it before dropping a reliable method such as the excellent Sturmdorf operation. We have found, as stated in our paper, that wide conization with suture combines the good points of the Sturmdorf operation with the desirable features of the cutting current.

Dr. Matthews' classification of the varying degrees of chronic cervicitis and the treatment applicable to each type is very helpful. Our cases fall under his third and fourth groups. He states that he has found the Sturmdorf operation gives excellent results. He has not tried wide conization and it is my hope that he will give it a trial for his broad knowledge and excellent contributions in this field are well known and his evaluation of results would be helpful to all of us.

(Additional papers presented at this meeting will be included in the February issue.)

in the modern attack upon the diseased cervix. Unquestionably good results will be obtained in some cases. The lasting cure of the diseased cervix and the removal of all of the diseased tissue can only be accomplished by removal of the entire cervix. Amputation, cauterization, and conization at best remove only part of the cervix and although the cervix may heal and look well from the outside, yet diseased tissue may well be buried behind the repair, amputation, or cauterization. If the cervix is truly diseased and needs wide conization it should be more safely handled by total hysterectomy with removal of the entire cervix. The fact that cancer of the cervix was found in eight cases (1.2 per cent) and cancer of the endometrium in eight cases (1.2 per cent) argues that (except for Dr. Crossen's good fortune) conization is not the proper treatment of the diseased cervix and the bleeding uterus.

It is my opinion, in these days of modern surgery, that cross cuts should be eliminated in favor of complete eradication of tissue that is so diseased that radical cauterization is deemed necessary. If patients are to have more children, it is better to do the simplest possible treatment as a palliative and, at a later date, when childbearing is over, a radical procedure removing all diseased tissue.

As I have the opportunity in after years to view cases of mine that had a conization, repair, or cauterization of the cervix, the fact is obvious that these operations simply buried diseased tissue; cystic areas can be seen bulging from behind the healed-over cervical epithelium. This sort of treatment must constitute a menace to patients and, in my own practice, I have had two such patients develop a cancer of the cervix. I believe that in a few patients this treatment can be considered but that for the great majority of patients with diseased cervixes total hysterectomy is far safer, more conservative, and much more protective.

I must confess that I do not agree with Dr. Crossen's treatment of the diseased cervix.

DR. JOSEPH L. BAER, Chicago, Ill.—I feel impelled to register a double-barreled comment, one in connection with the interesting compilation presented by Dr. Crossen and one in connection with the comments just read and emanating from Dr. Meigs. I have found cauterization to be completely adequate for all the minor types of visible cervical lesions excepting those which under biopsy proved malignant. This refers to the ordinary erosions, the tremendously hypertrophied erosions, and multiple Nabothian cysts of all sizes. For all of these conditions, I have found the actual cautery to be completely adequate. Our procedure has been, and is, a thorough cauterization in a single sitting, in the office and without anesthesia, the patient being ambulatory thereafter, and being observed for four to six weeks thereafter until the entire cauterized area is thoroughly healed.

The number of hemorrhages, occurring usually at the time of separation of the slough, has been so small as to be completely negligible and completely controllable in the office. There have been no symptom-producing strictures of the cervical canal. The number of strictures of the external os has been exactly two. Each was relieved by office dilatation.

For the very severe, markedly hypertrophied cervixes with deep bilateral lacerations, i.e., truly diseased cervixes, it is entirely appropriate to do the Sturmdorf operation. In that operation a suture placed bilaterally on the descending branches of the uterine arteries completely controls the bleeding and brings about easy and relatively dry repair of the Sturmdorf type. When there is uterine pathology, it is desirable to remove the cervix with the uterus. We have gone almost entirely from supravaginal hysterectomy to total hysterectomy.

DR. CROSSEN (Closing).—There seems to be some confusion as to the type of case in which wide conization is indicated. We use it in cases of extensive chronic cervicitis with deep-seated cysts, such as the cases described in groups three and four of Dr. Matthews' classification. These are the cases in which we formerly did the Sturmdorf operation. Wide conization is a hospital procedure and it cannot be compared with office cauterization which is used in less extensive cases.

Dr. Meigs' discussion is not only a condemnation of wide conization but applies equally to any cervical operative procedure designed to remove the affected area. Nearly one-half of the patients in our series were in the child-bearing period. They wished to be relieved of the troublesome discharge and the menace of future carcinoma, and yet wished to preserve the

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- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, James R. Bloss, Huntington, W. Va. *Secretary*, Leroy A. Calkins, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 7-9, 1949.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, S. R. Norris, Jacksonville, Fla. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Williamsburg, Va., February 10 to 12, 1949, at the Williamsburg Inn and Lodge.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
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- Obstetrical Society of Philadelphia.** (1868) *President*, Carl Bachman. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Herbert E. Schmitz. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
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- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Stanley T. Garber. *Secretary*, Joseph G. Crotty, 146 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James Hodgkiss. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, Paul Gustafson. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
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- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Woodard D. Beacham. *Secretary*, Harry Meyer, 3439 Prytanía St., New Orleans, La. Meetings held October, November, January, March, and May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

Items

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 4, 1949.

Arrangements will be made so far as is possible for candidates to take the Part I examination (written paper and submission of case records) at places convenient for them. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held May 8 to 14 inclusive, 1949, at the Hotel Shoreland, Chicago, Illinois. Notice of the exact time and place of the Part I and Part II examinations will be sent all candidates well in advance of the examination date. Closing date for reapplications for admission to the Part II examination will be April 1, 1949.

New Bulletins are now available for distribution upon application and give details of all changes in Board requirements and regulations made at the annual meeting of the Board held in Washington, D. C., May 16 to May 22, 1948. These relate both to candidates and to hospitals conducting residency services for training.

Application forms and Bulletins are sent upon request made to

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The following physician is to be included in the list of Diplomates certified by this Board:

Whitely, James Meacham, 508 Medical Arts Building, Portland, Oregon, born 1913, received M.D. from University of Oregon in 1938.

PAUL TITUS, M.D.,
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- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Charles F. Moon. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Gerald Rogers. *Secretary-Treasurer*, Arthur A. Hellbaum, 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
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- Oregon Society of Obstetricians and Gynecologists.** *President*, Duncan R. Neilson. *Secretary-Treasurer*, David M. Baker, 520 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, A. D. Cook. *Secretary*, L. O. Frederick, 413 Third National Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Moses Cohen. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held third Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, Walter Simmons. *Secretary*, Richard H. Street, Jr., The Street Clinic, Vicksburg, Miss. Meetings held semiannually.
- Florida Obstetrical and Gynecological Society.** *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, Manly E. Hutchinson. *Secretary*, J. Decherd Guess, 200 E. North Street, Greenville, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
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- St. Louis Gynecological Society.** (1924) *President*, A. N. Arneson. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Warren E. Massey. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Raymond J. Pieri. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
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- Seattle Gynecological Society.** (1941) *President*, Donald J. Thorp. *Secretary-Treasurer*, Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *Secretary*, Warren W. Tucker, 1820 Gilpin St., Denver 6, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Henry A. Sincock. *Secretary-Treasurer*, Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, P. L. Martin. *Secretary*, Albert P. Kimball, 233 "A" St., San Diego, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Walter McMann. *Secretary-Treasurer*, L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Dana Cox. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, H. J. Lesnick. *Secretary*, Mark Daniel, 2344 Davidson Ave., Bronx 53, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Joseph G. Webster. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, L. G. Baldwin. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, William A. Scott. *Secretary*, James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, S. B. Conger. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Society of Obstetrics and Gynecology.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

(Figs. 1 and 2.) In this case a mass of hemangiomatous channels pervades all of the myometrium. In two other instances the hemangioma was found only in the lower third of the corpus. In each case the uterine veins were huge and tortuous. I have no way of telling in what way the two conditions are linked. However, the presence of huge pelvic varicosities involving mainly the uterine circulation and the progressive intensification of pelvic symptoms over a period of years hints at an acquired factor. We expect to describe this condition in greater detail in the near future.



Fig. 1.



Fig. 2.

Fig. 1.—Corpus Uteri, 10 by 7 by 7 cm. Progressive severe dysmenorrhea and menorrhagia. Nullipara, aged 35 years. Preoperative diagnosis: adenomyosis.

Fig. 2.—Cavernous intercommunicating bloodspaces lined with a single layer of endothelial cells permeate the entire myometrium.

DR. TAYLOR (Closing).—Both the discussers and I myself have appealed constantly to the past. This has been necessary because the concept which has been presented is not today a conventional one. Consequently, while this material was being worked up, the literature was gone over carefully to find as many supporters as possible for this thesis.

Actually, this subject is one which is very modern and one which in most branches of medicine is being actively investigated. I refer particularly to the vast group of disorders that are being studied under the general term of psychosomatic medicine. It has come to be believed that various types of disorder are due to the effects of emotion upon the smooth muscle of hollow viscera and blood vessel walls. In many of these other areas, methods of precision are gradually being developed and the factors affecting vascular and intestinal function are being measured. We are at a point where we may soon be able to apply similar concepts and methods to explain menstrual and other gynecologic symptomatology.

the vessels, the excitation of the lymph tracts that discharge the lymph, is sufficient to produce inflammation without an infection. This may readily proceed to a true fibrosis which is described by the essayist.

I tend to discredit the endocrine factor in producing this congestion syndrome. It is interesting to note that while the older literature was scattered, that is due simply to the fact that each man wrote upon the subject that he was engaged in studying at the moment. To Dr. Taylor we owe the whole putting together of this syndrome, except that he left out the headache and the indigestion, which is probably also due to the same cause.

Lastly, I should like to point out that while the essayist has noted that major surgery is much decried, in Dr. Taylor's whole series of patients but one was classified as completely cured and that was by hysterectomy.

DR. WILLARD R. COOKE, Galveston, Texas.—We should be grateful to Dr. Taylor for reviving a concept of real importance which, as we all know, has more or less lapsed from our gynecologic consciousness. My own interest dates to the early years of association with a Chief who, as was customary in those days, operated on all cases of retroversion. In attempting to find out why the majority of these patients had no symptoms, I finally became convinced, to a reasonable degree of certainty, that the symptomatology varied directly with the degree of congestion and the resultant changes in the tissues drained by the veins involved. Later, a correlation was established between congestion originating in the genitals and symptoms referable to adjacent viscera. The best example in this group is the vesical symptomatology so frequently seen in connection with fibromyomas and commonly attributed to "pressure" of a nodule upon the bladder. Almost unbelievable distention of the bladder commonly occurs without vesical symptomatology: whereas the entire subjective symptomatology may be referred to the bladder in cases of very small nodules contiguous to it. Cystoscopy discovered that the vesical symptomatology was in direct proportion to capillary and venous engorgement in the wall of the bladder, not always contiguous to the fibromyoma. Still later, a relationship between genital congestion and symptomatology, and dysfunction and disease primary in adjacent viscera was reasonably established, the most familiar example being in cases of the spastic colon-colitis sequence. Finally, circulatory disturbances due to endocrine and psychic factors were subjected to study.

In regard to the tissue changes brought about by long-maintained congestion, we are in full accord with Dr. Taylor, very definitely so in the case of fibrosis of the ovary. We feel that the concept of "replacement fibrosis," long held in contempt by pathologists, should be revived. We are less certain as to the uterus, because of the extreme variability of the histologic characteristics in the enlarged uteri which he describes. In fact, we are so much at sea that in our laboratory we call them merely "big uteri." I must confess that we have never attempted to correlate genital congestion with coccydynia.

From the clinical aspect, especially in private practice, we have found that the commonest cause of pelvic congestion and its sequelae lies most often in the spastic colon-colitis sequence; next in the sedentary life, the most spectacular cases being seen in the high school athlete who is suddenly transferred to the physical inertia of the life of the typist, the telephone operator, or the wife of a well-to-do husband. Next in some order come the cases of physical genital disease, of suppressed or frustrated libido, and of many other abnormalities.

Altogether, the concept of circulatory disturbances is one which deserves further recognition and investigation.

DR. LUDWIG A. EMGE, San Francisco, Calif.—In connection with Dr. Taylor's interesting discussion of vascular disturbances of the female reproductive organs, I like to present a vascular disturbance of the uterus infrequently met with. Cavernous hemangioma of the myometrium, as far as I know, has not been diagnosed preoperatively probably because the symptomatology simulates uterine adenomyosis. The rarity of the condition is evidenced by the fact that in our extensive pathologic material only three instances of hemangioma of the uterus have been encountered. The specimen presented here is the most typical seen by me.

similar to diverticulitis of the colon with abscess formation. When the urethral orifice of the diverticulum is closed by an inflammatory process, then incision and drainage through the anterior vaginal wall may be sufficient for cure. Diverticula of the urethra never contain all the normal layers of the urethra. The sac has a mucosal lining; this, however, may be necrotic or ulcerative and difficult to identify. Further evidence that urethral diverticula are congenital in origin is found in the fact that some are of a large size, perhaps as long as the urethra and 1 cm. in diameter and yet there is no history that an abscess has been present in the region. From many of these urine can be expressed freely and it usually has an ammoniacal odor.

Another reason why I cannot agree with the usual theory concerning these diverticula is that I am skeptical regarding the presence of glands in the female urethra. I am inclined to agree with Cabot¹ that the urethra is devoid of glands except for Skene's glands located on each side of the external urethral meatus. I am equally certain that these Skene's glands have no connection whatever with these diverticula. I agree that infection has a definite role in the symptomatology and that the symptoms depend entirely on the degree of infection, which may be a low-grade infection or an acute abscess. But I doubt whether the infection has much to do with the development of the diverticulum. About 30 per cent of all women have some degree of urethritis, granular, cicatricial, or cystic. This incidence of infection can be easily, and I believe correctly, explained on the basis of the exposed position of the urethra.

Trauma to the urethra and infection, I believe, are most commonly the exciting etiologic factors in the production of symptoms referable to a urethral diverticulum. Trauma results from coitus and childbirth. In my series of 71 surgically treated cases, all except five of the patients were married and 80 per cent had had children. In only three cases had Neisserian infection been present, so that the inflammatory process in this group must be classed almost exclusively as nonspecific. For this reason, I believe that in the future the diverticulum with abscess should be regarded as a nonspecific lesion unless proved to be otherwise.

The average age of the 71 patients was 41 years. Thirty patients were from 31 to 40 years of age; 27 from 41 to 50 years of age; 6 were 30 years of age or less and 8 were more than 50 years of age. None of the patients were children.

Symptoms

The duration of symptoms is important. Symptoms may exist for only a few weeks, and can last for thirty-three years or more, as in one of my cases. Most of the patients in my group had symptoms for more than five years; the usual story was five to ten years. The cardinal symptoms were pain and frequency of urination, leakage of urine, dyspareunia and, finally, a vaginal mass.

The urinary symptoms may be mild to severe. Often the urethra does not show any local inflammation at all but the voided specimen will contain large amounts of pus even though contamination from the vagina is excluded. The catheterized urine may be entirely negative and this fact may lead to a mistaken diagnosis. On account of the symptoms of urethritis and without much evidence of anything else, the urethras of most of the 71 patients in my group had been excessively treated with local applications, heat, and tampons.

URETHRAL DIVERTICULUM IN THE FEMALE: A CLINICAL STUDY*

VIRGIL S. COUNSELLER, M.D., ROCHESTER, MINN.

(From the Division of Surgery, Mayo Clinic)

DIVERTICULA of the female urethra are not common, nor are they actually uncommon. The symptoms appear bizarre and yet they are diagnostic when carefully studied. It seemed to me, with these facts in mind, that the findings in 71 cases of diverticulum of the female urethra in which surgical treatment was employed at the Mayo Clinic and the impressions formed from study of these cases would be of interest to this association. A much larger group of patients who had small sacculations, deformities, and postoperative irregularities or scars which responded to local treatment and dilatations of the urethra were studied, but data on these patients are not included in this report.

This lesion has been known for many years but practically nothing on this subject appears in the current gynecologic literature. Most of the references to it and its management have been made by urologists and by some gynecologists who have written textbooks on gynecology which include some excellent discussions on urology of the female. Kelly⁵ discussed this lesion in his textbook under the subject of suburethral abscess and also alluded to it as a "urethral urinary pocket" and urethral diverticulum. He described it as a pus pocket in the urethrovaginal septum from which pus was discharged by a slit in the posterior part of the urethra. Te Linde⁷ and Wharton⁸ presented excellent drawings of the lesion and its surgical management. Polak,⁶ in his manual of gynecology, referred to it also as a suburethral abscess. Curtis² grouped diverticula and abscess pockets together and his statement regarding them is significant. He said, "Diverticula and abscess pockets connected with the urethra may have the same etiology. I have been gradually brought to this view through interest in the anatomy of the anterior vaginal wall. Let us not assume that abscess pockets are rare, for they are quite common indeed and most often they occur as sequelae of gonococcal infections." Furniss³ has written, I believe, the most descriptive article on this subject and he included abstracts of the histories and findings in his ten cases. Herman and Greene,⁴ in 1944, presented in detail the figures on incidence of the lesion and gave a good description of the symptoms and diagnosis. They reported six additional cases.

My studies of this lesion have caused me to believe that it is much more common than was previously believed and I have formed some impressions about its management which I wish to present briefly.

Most authors apparently have concluded that these diverticula are sequelae of repeated infections in a urethral gland and most likely are Neisserian in origin. After dissecting out a good number of these diverticula, I am of the opinion that they originate as congenital defects of the urethra and are subsequently influenced by trauma and nonspecific infections. They are analogous to diverticula of the intestinal tract or bladder in that they do not cause trouble unless they are unable to evacuate their contents completely. Any diverticulum that cannot empty itself will become infected and produce an abscess. Diverticula of the colon are excellent examples. A suburethral abscess to me is

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excision of the diverticulum and repair of the urethra. This can be accomplished in practically all cases except the few in which abscesses are present. In these few instances, the orifice of the diverticulum may be necrotic and cannot be closed by suturing. A urethral fistula then would result and this fistula should be repaired only after all evidence of inflammation has subsided. When the inner wall of the diverticulum extends posteriorly along the urethra, it usually is intimately attached to the urethra and no attempt should be made to separate the wall of the diverticulum from the urethra. To do so may cause multiple fistulas.

Surgical excision may be difficult unless the diverticulum can be seen readily. A retention catheter, No. 18 to 22, should be placed in the bladder as a preliminary procedure, so that the identity of the lumen of the urethra is always known. The anterior vaginal wall should be mobilized, preferably between two small clamps or hemostats and the anterior vaginal wall should be opened from just behind the external urethral meatus to the area of the trigone of the bladder. The fascia over the urethra is incised and separated from it and the vaginal wall, as in repair of urethrocele. As the surgeon cuts with a sharp scalpel directly down on the urethra, the diverticulum as a rule begins to bulge into view. With the catheter in place in the urethra, the diverticulum can be distinguished from the urethra. At this point the diverticulum can be grasped with a clamp and further separated from the surrounding tissues.

When the diverticulum is definitely identified, it should be opened and its contents, if any, evacuated. The extent and direction of the sac can be accurately determined by examination of the interior of the sac under direct vision. The relation of the inner wall to the urethra can be observed. If the diverticulum is firmly adherent to the urethra and at all inflammatory, all of the sac should be excised except that small segment along the urethra. The orifice in the urethra can be closed with interrupted fine catgut sutures. This region should be reinforced by a running suture which closes the fascia over the entire urethra including the defect. A catheter is maintained in the urethra for only four to five days; the patient then is advised to go to the bathroom and void. Subsequent catheterizations are inadvisable.

Urethrovaginal fistulas which occur subsequent to repair of cystocele, urethrocele, or vaginal hysterectomy could easily be due to a urethral diverticulum which was overlooked previously. I cannot tell from my studies on fistulas which ones may have been caused in this manner but I strongly suspect that the number is greater than physicians may have thought previously.

Comment

Diverticula of the female urethra in all probability originate from congenital defects in the urethra just as do diverticula in any other part of the body. They may be quiescent, but if nonspecific infection and trauma disturb them in any way, symptoms develop. The exposed position of the female urethra and the high incidence of nonspecific urethritis make it likely that, if a diverticulum is present, it will sooner or later produce symptoms and require surgical excision for a cure. These conclusions are formulated on the basis of 71 patients who have been treated surgically.

References

1. Cabot, Hugh: *Proc. Staff Meet. Mayo Clin.* 11: 589, 1936.
2. Curtis, A. H.: *A Textbook of Gynecology*, ed. 5, Philadelphia, 1946, W. B. Saunders Company, p. 659.
3. Furniss, H. D.: *J. Urol.* 33: 498, 1935.
4. Herman, Leon, and Greene, L. B.: *J. Urol.* 52: 599, 1944.

Pain is a significant symptom and its presence should make the physician at least suspect the presence of a diverticulum of the urethra. It is of 4 types: (1) low abdominal or suprapubic, like that usually produced by cystitis; (2) perineal, which appears to extend down through the perineal region and rectum; (3) vaginal, which usually consists of a sense of pressure or weight in the vagina; and (4) pain which frequently darts upward from the urethra and through the vagina to the pelvic organs. Pain in the sites and types described appeared in 55 per cent of the 71 cases.

Leakage of urine or a discharge from the urethra was noted in 40 per cent of the cases. Some patients considered this condition a stress incontinence. The characteristic leakage is that which immediately follows urination, when the patient thinks she has completely evacuated her bladder and is surprised to find a subsequent involuntary discharge of a small amount of urine.

Dyspareunia was experienced by 10 per cent of the patients and was a complaint of those who had rather acute inflammatory reactions in the anterior vaginal wall.

A mass in the anterior vaginal wall was noted by 40 per cent of the patients. These masses were not all abscesses and surprisingly enough were not always especially tender. The mass may be urine, pus, and sometimes multiple calculi. If the history indicates that a diverticulum has been present for a number of years, there often will be a sense of pressure in the vagina and the anterior vaginal wall may be indurated. This induration may simulate a mass but a true mass may not be present.

The severity of the complaint is also significant. It is out of all proportion to that which the physical findings concerning the urethra indicate should actually be produced. There is no relation between the complaint and menstruation.

Diagnosis

Vaginal examination with careful palpation of the anterior vaginal wall under the entire urethral region may reveal some induration or a definite mass. Pressure on the mass will cause foul-smelling urine or pus to exude from the external urethral orifice unless the orifice of the diverticulum has been occluded by the inflammatory process. If there is only induration, the diverticulum can be more easily identified if a urethroscope is placed in the urethra and then the urethra is palpated over it.

Cystoscopy is not always successful in identifying the diverticulum. The orifice sometimes is not easily seen. In one case, cystoscopy was performed seven times before the orifice of the diverticulum could be seen and several have had cystoscopic examinations more than one time. There may be more than one opening to the diverticulum. The opening is usually in the middle third of the urethra and in the midline. However, in some of the 71 cases the opening was on one or another side of the midline. The diverticulum may extend in any direction along the urethra and occasionally almost encircle it. In a few cases, the orifice of the diverticulum was in the posterior portion of the urethra and the diverticula were situated under the trigone of the bladder. When the orifice can be identified, a small lead catheter should be coiled in the diverticulum and a roentgenogram taken of it. Also, injection of an opaque medium into the diverticulum, if possible, followed immediately by a roentgenogram aids considerably in determining the size and direction of the diverticulum.

Treatment

It has been our experience at the clinic that any local treatment, such as massage, dilatation, or instillations, is of no value when a real diverticulum exists. Transurethral incision of very small diverticula for more adequate drainage may be useful. The best treatment, however, is complete surgical

Dr. Counsellor's large series of 71 cases, in which surgical treatment was employed, probably the largest series reported, allows him to speak with authority on the subject.

DR. LAWRENCE R. WHARTON, Baltimore, Md.—Dr. Counsellor's paper falls into two parts—the first dealing with the anatomic findings and his conclusions about etiology; and the second, with the clinical discussion.

Dr. Counsellor's anatomic findings are interesting. Probably many women have small periurethral diverticula or crypts which are the foci that perpetuate chronic infections of the urethra and bladder. Some of these diverticula become large. The small ones are extremely hard to find, the large ones can be discovered easily by palpating the periurethral regions and by expressing the large quantity of pus, much more than would be contained in the urethra itself.

Whether these are all congenital diverticula or whether some begin as infected periurethral glands, is perhaps an academic question as far as therapy is concerned. Dr. Counsellor does not believe there are normally any glands around the urethra, and hence leans toward the opinion that these diverticula do not originate in such normal structures.

The female urethra is a remarkable structure. It looks so simple. It is short, straight, and has a large caliber. And yet careful observers have reached contradictory opinions about its normal anatomy, especially about the presence of glands in its walls, with openings into the urethral lumen. I myself doubted the existence of periurethral glands (excluding Skene's), until I read the article by Dr. Huffman presented before this Society one year ago. It is difficult to doubt the existence of periurethral glands after studying Dr. Huffman's work.

If there are normally such glands around the urethra, then there is no reason why such glands should not behave as glands do anywhere else, become infected, distended by the occlusion of their ducts, and transformed into cysts. In other words, one does not have to assume that all diverticula are congenital, if one accepts the proposition that there are usually small glands in the urethral wall.

Consequently, I would be inclined to modify Dr. Counsellor's view, and state that these diverticula may be either congenital or acquired, and that the small multiple crypts and diverticula probably originate in periurethral glands.

I do not believe it is possible to distinguish congenital from acquired diverticula by clinical means, with absolute certainty. This would apply especially to such conditions when they occur in adults, and all of Dr. Counsellor's cases were in adults. Fortunately, a few such cases have been found in infants and children. Dr. Thos. S. Cullen published a paper on "Urethral Diverticulum" in 1894. Dr. Cullen had abstracted the literature and found several cases in children—one in an infant 1 year old. Such observations naturally lend weight to Dr. Counsellor's view that they are congenital, although it does not exclude the possibility that some may be acquired.

The discussion concerning their origin may be possibly academic but there is nothing academic about the clinical problem they present. The persistence of these infected diverticula and the diagnostic difficulty are shown by our experience. I am certain that in a considerable number of women, chronic recurring cystitis is due to these insidious urethra lesions. I am equally certain that I have missed the diagnosis in a good number. Some of these women have wandered from clinic to clinic, trying to find the cause of their cystitis, without success, for we have all missed these small urethral lesions. Dr. Counsellor says that his patients have had symptoms for five to ten years, on the average, and that he has cystoscoped some of them nine times before finding the diverticulum. This is a general experience.

DR. N. SPROAT HEANEY, Beverly Hills, Calif.—There is one symptom that I think is pathognomonic, and that is the feeling that the patient has for a short time after voiding. While urinating, she fills up the diverticulum and then the diverticulum will slowly empty and the patient gets wet.

A point also to observe is that, if the patient voids before examination and you strip the urethra, as you ordinarily do to see whether there is pus in the urethra, you will milk out a half teaspoon or so of urine flecked with pus. That, I think, is the most important finding leading you to suspect that there is a diverticulum of the urethra.

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6. Polak, J. O.: *A Manual of Gynecology*, ed. 2, Philadelphia, 1922, Lea & Febiger, p. 370.
7. Te Linde, R. W.: *Operative Gynecology*, Philadelphia, 1946, J. B. Lippincott Company, pp. 656-657.
8. Wharton, L. R.: *Gynecology, With a Section on Female Urology*, ed. 2, Philadelphia, 1947, W. B. Saunders Company, p. 346.

Discussion

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Counsellor's report is based on 71 cases of diverticulum of the female urethra in which surgical treatment was employed at the Mayo Clinic. Contrary to the opinion of most authors on the subject who imply that diverticula are the result of repeated infections in a urethral gland, due largely to Neisserian invasion, Dr. Counsellor believes that they originate as congenital defects of the urethra, which are subsequently affected by trauma and nonspecific infections. He further compares a suburethral abscess to diverticulitis of the colon with abscess formation. He strengthens his point against the acceptance that a diverticulum develops as the result of infection of a urethral gland by the statement that the female urethra is devoid of glands, other than Skene's glands, one of which is found on each side of the urinary meatus. I am in agreement with him in the above contentions, and also in the fact that Skene's glands have no relation to these diverticula. Trauma from coitus and childbirth and infection are held to be the common exciting etiologic factors referable to urethral diverticula.

As to the symptomatology, the essayist lists pain, urinary frequency, leakage of urine, dyspareunia, and vaginal mass. The opening of the diverticulum in the urethra is stated to be in the middle third of the urethra, in the middle line.

Dr. Counsellor states that diverticula of the female urethra are not common, nor are they actually uncommon. On the basis of my own experience, I have always considered this disorder to be quite uncommon. A review of the records at the Carney Hospital, from June, 1937, to September, 1947, showed only four cases during approximately ten years.

CASE 1.—A woman, 35 years of age, mother of three children, who had an infected diverticulum of the urethra and a cystocele. The diverticulum was resected, the urethral opening closed, the cystocele repaired, and constant bladder drainage instituted. There was satisfactory healing and the patient was discharged cured.

CASE 2.—A married, nulliparous woman, 35 years of age, had an infected diverticulum of the urethra and uterine fibromyomas. Operation was performed on May 13, 1938, and consisted of resection of the diverticulum and reconstruction of the urethra over a catheter, this being unsuccessful. There followed four operations in an attempt to close the resulting fistula. All failed because of the great loss of urethral tissue at the first operation. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were subsequently performed for fibromyomas of the uterus, pelvic inflammatory disease, and endometriosis. On Sept. 16, 1943, the left ureter was transplanted in the sigmoid. On Sept. 9, 1944, the right ureter was transplanted in the sigmoid. In July, 1947, intravenous pyelograms showed the kidneys in satisfactory condition. The patient had urinary control and the nonprotein nitrogen was 28 to 40 mg. per cent. Examination made in April, 1948, showed the physical condition to be satisfactory.

CASE 3.—This was the case of a married, nulliparous woman, 58 years of age, with an infected urethral diverticulum. The sac was dissected, opened, and the contents evacuated. The sac was resected, the urethral opening closed and the anterior vaginal wall sutured. Constant drainage was established. The healing was satisfactory and the patient was discharged cured.

CASE 4.—A married woman, 31 years of age, mother of three children, all delivered by cesarean section, had a diverticulum of the urethra. Operation consisted of excision of the diverticulum, conserving a strip 1 cm. in width from the sac. The opening in the urethra was closed in three layers, using the strip dissected from the diverticulum as a third layer in closing the defect. The anterior vaginal wall was sutured and suprapubic bladder drainage instituted. Satisfactory healing took place, and the patient was discharged cured.

The configuration and level of attachment of the peritoneal reflections or fossas varies considerably. When exposed by dissection, the parietovesical reflection usually lies symmetrically over the bladder. Most often it presents a downward convexity (Fig. 2a, c) but occasionally the convexity faces upward (Fig. 2b). If the paravesical reflections differ in their level of attachment, the parietovesical reflection is correspondingly asymmetrical (Fig. 2d). The uterovesical reflection ordinarily extends lower on the bladder than the parietovesical reflection (Fig. 2a, b); but the reverse relationship may exist (Fig. 2c). In our experience, the uterovesical reflection always lies in a fairly even transverse manner over the lower uterine segment. The general level of peritoneal attachment may lie much higher or much lower on the bladder than shown in Fig. 2.

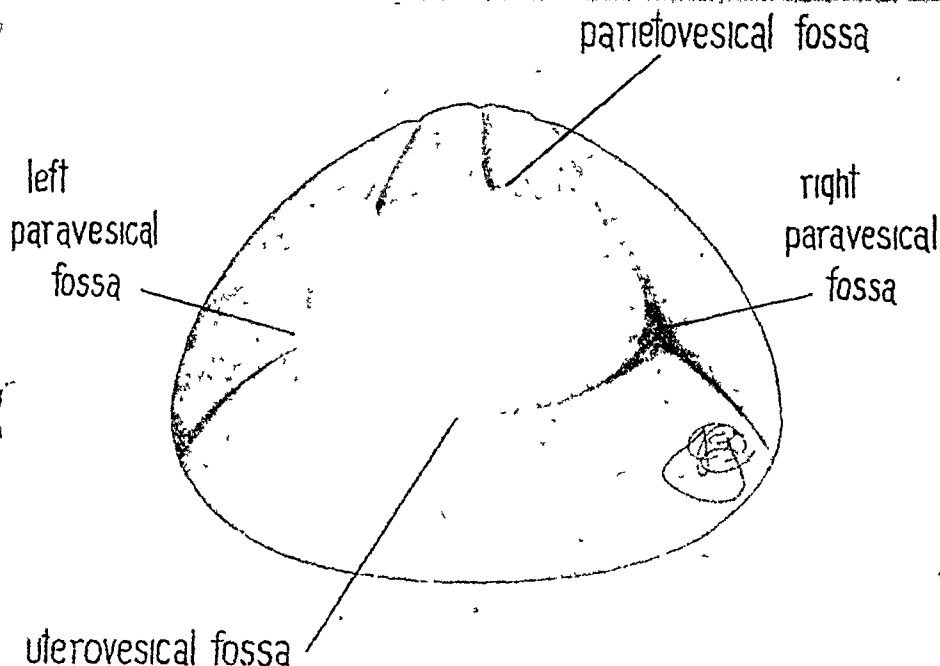


Fig. 1.—The peritoneal aspect of the structures encountered in extraperitoneal cesarean section (abdominal wall, bladder, urachus, lateral umbilical ligaments and lower uterine segment). The partially distended bladder brings out the peritoneal fossas. This figure approximates the area of peritoneum and fascia separated in forming the peritoneofascial flap.

The outer connective tissue layer of peritoneum exhibits a fibroareolar nature varying in thickness and density according to location and the individual (Fig. 3); it contains varying amounts of adipose tissue.

Anteriorly subserous or fibroareolar peritoneum is applied to the transversalis fascia covering the recti muscles. It is more areolar than fibrous in character and may contain properitoneal fat. In the midline of this layer, the terete fibrous urachus, a remnant of the embryonic allantois, extends from the vertex of the bladder to the umbilicus.

Over the bladder dome, or supravescical area, areolar tissue may predominate (Fig. 3a, a')—a condition greatly simplifying extraperitoneal cesarean; but it is usually absent to some extent (Fig. 3b, b', c, c'), with the result that, for clinical purposes, a varying area of serous peritoneum is inseparable from perivesical fascia. In direct proportion to its degree and extent, adherence of these structures increases the formidability of operation.

Original Communications

THE SURGICAL ANATOMY OF EXTRAPERITONEAL CESAREAN SECTION

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THE aim of extraperitoneal cesarean section is adequate exposure of the lower uterine segment for delivery of the child without accidental injury to the peritoneum, bladder, or ureters. Because the technical difficulty of the procedure is governed largely by the anatomic variations encountered, knowledge of the regional anatomy and its vagaries is important.

The material presented in this essay results from experience with forty-nine extraperitoneal operations of all major types: the Latzko,¹ and Latzko as modified by J. C. Irwin² and J. F. Norton,³ the Waters⁴ and the technique described. Five operations were performed in the absence of labor, one at six and one-half months' gestation, and the others approximately at term. Three were secondary cesareans following one primary extraperitoneal and two primary transperitoneal procedures. The peritoneal staining technique devised by one of us⁵ facilitated the study of anatomic variations in twenty-one operations, and in all the above methods except the Latzko.

For complete exposition, the material is presented from four interlocking points of view: anatomic description, planes of dissection, anatomic approaches to the lower uterine segment, and the technique developed from consideration of the foregoing.

Anatomic Description

Modern extraperitoneal cesareans are ideally accomplished by separating the intact peritoneum with portions of its enveloping fascia from the anterior abdominal wall, bladder, and lower uterine segment. The resulting structure is termed the *peritoneofascial flap*, and during its dissection two components, the anterior (parietovesical) and posterior (utero-vesical) transverse peritoneofascial folds may usually be recognized. Fig. 1 depicts the approximate area of peritoneum and fascia detached in forming the peritoneofascial flap.

1. *The Peritoneum*.—The peritoneum is composed of an inner layer of simple squamous epithelium or serosa, and an outer subserous layer of fibroareolar connective tissue.^{6, 7, 8} The serosa descends from the dome or supra-vesical area of the partially distended bladder to form (Fig. 1) a parietovesical peritoneal reflection anteriorly, right and left paravesical reflections laterally, and a utero-vesical peritoneal reflection posteriorly.

vesical fascial fold, the urachus, which may be patent, arises from the perivesical fascia and proceeds in the areolar subserous peritoneum, just anterior to the serous peritoneum, to the umbilicus.

The perivesical fascia is intimately coapted to bladder muscularis throughout and in the supravescical area, where it may be exceedingly thin, it is often just as closely coapted to varying areas of serous peritoneum (Fig. 3b, b', c, c'). It has been observed in most operations performed with the peritoneal staining technique that in such areas the perivesical fascia may be so thin that bladder and serous peritoneum can be separated only by dissection in the outer layers of vesical muscularis. This fact is not, however, a valid reason for performing the major portion of the dissection in that plane.

Posteriorly, the perivesical and periuterine fascias blend loosely inferior to the uterovesical peritoneal fold to take part in forming the posterior (uterovesical) transverse peritoneofascial fold. Here the serous peritoneum is attached by loose areolar tissue to the plane of junction of these fascias and adherent posteriorly to periuterine fascia, while it may or may not be adherent anteriorly to the perivesical fascia.

Lateral to the bladder on either side and inferior to the paravesical fossa lies the paravesical space. During the last trimester of gestation it roughly approximates an inverted three-sided pyramid bounded superiorly by the peritoneum of the paravesical fossa, medially by the membranous perivesical and posteriorly by the membranous periuterine fascias, and anterolaterally by the fascias of the abdominal and pelvic walls. It contains abundant fibroareolar tissue derived from the fascial structures forming its boundaries, and along the junction of the perivesical and periuterine fascias lies a constant mass of adipose tissue—the so-called yellow chicken fat. An inferior extension of the paravesical space contains the ureter as it emerges from the bladder to course laterally, posteriorly and superiorly along the pelvic wall. A posterolateral extension of the paravesical space contains the iliac and uterine vessels, and again the ureter. As performed in modern extraperitoneal operations, dissection of the paravesical space rarely exposes either blood vessels or ureter; however they can be demonstrated after the uterus has been emptied.

Planes of Dissection

In describing their technique, early operators implied use of a plane of dissection between the peritoneum and bladder. As might be expected from their limited knowledge of the regional anatomy, these surgeons regarded extraperitoneal cesarean as a theoretically ideal but impracticable operation.

In 1940, Waters popularized a satisfactory cleavage plane between perivesical fascia and bladder muscularis. Its particular disadvantage lies in disruption of bladder vessels with annoying though not serious bleeding, in exposure of bladder mucosa and occasional violation of the bladder cavity. Furthermore this cleavage plane does not eliminate accidental opening of the peritoneum.

In 1942, Ricci and Marr⁹ advocated dissection within the layers of the perivesical fascia. This plane of cleavage would be ideal if it could be consistently pursued; but the intimate union of serous peritoneum, a thin perivesical fascia and vesical muscularis often encountered in the supravescical area prevents consistent use of this plane of dissection alone.

There are anatomic limitations to any single plane of dissection. In the first place, dissection of the paravesical space, which must be cleared to provide the exposure requisite to any modern extraperitoneal cesarean technique whether initiated by way of the anterior (paravesical) or medial (supravescical) approach to that space, is neither within the layers of the perivesical fascia nor between

Loose areolar tissue separates the serosa of the uterovesical fossa above from the junction of the perivesical and periuterine fascias below; this is the site of initial incision for the bladder flap when performing low cervical transperitoneal cesarean section. When the anterior border of this area exhibits adherence of serous peritoneum to perivesical fascia, a definite posterior transverse peritoneofascial fold is formed. Along the posterior border of this area, serous peritoneum is attached to periuterine fascia with the intervention of minimal areolar and no adipose tissue; in our experience, this is the only constant area of adherence.

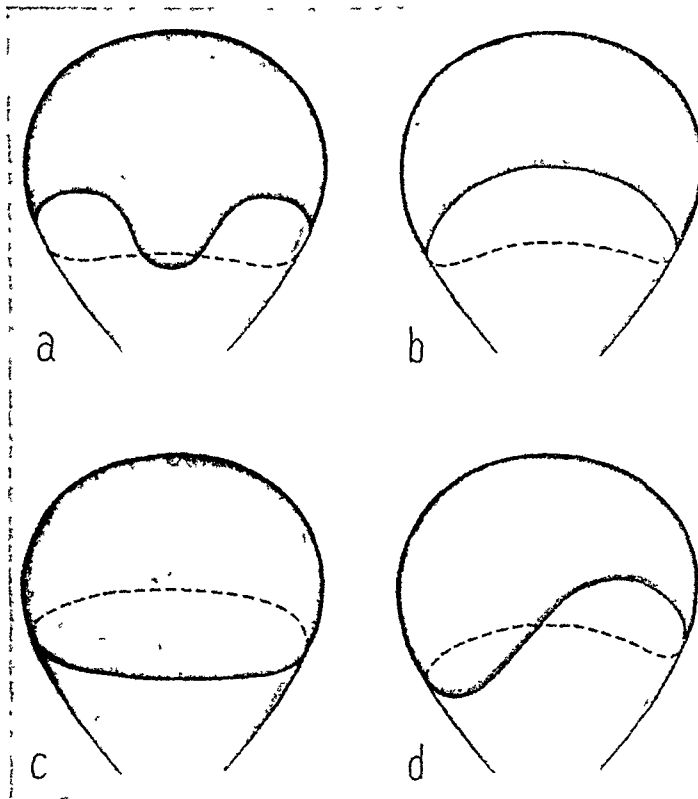


Fig. 2.—Variations in configuration of the peritoneal bladder reflections. *a* and *c* Common downward convexity of the anterior or parietovesical reflection. *b*: Uncommon upwardly convex parietovesical reflection. *d*: Rare asymmetrical parietovesical reflection. The posterior or uterovesical reflection lies symmetrically in a transverse manner over the lower uterine segment; it usually extends lower on the bladder than the parietovesical reflection (*b*) but the reverse relationship may exist (*c*).

2. The Fascias.*—The transversalis fascia lining the musculature of the lower abdominal wall extends into the pelvis as endopelvic fascia. This provides fascial covering for the parietal pelvic walls and forms membranous envelopes about the bladder, ureters, and uterus: the perivesical, periureteral and periuterine fascias, respectively.

The transversalis and anterior perivesical fascias blend intimately inferior to the parietovesical peritoneal fossa, to take part in formation of the anterior (parietovesical) transverse peritoneofascial fold. The round, fibrous, lateral umbilical ligaments (obliterated hypogastric arteries), running from the anterolateral aspects of the bladder to the umbilicus, mark the lateral boundaries of this fold. In the midline, a short but variable distance posterior to the parieto-

*As employed in this essay, the term "fascia" denotes visible and palpable sheets of connective tissue as they are encountered at the operating table.

In fact, it is fairly certain that most extraperitoneal cesareans are performed successfully only by the planned or chance use of several planes of dissection.

Anatomic Approaches to the Lower Uterine Segment

Most modern extraperitoneal cesarean techniques provide bilateral exposure of the lower uterine segment adequate for a low transverse cervical or low vertical incision. There are only two possible initial paths of approach: by the paravesical space (the paravesical approach) or by the anterior transverse fold

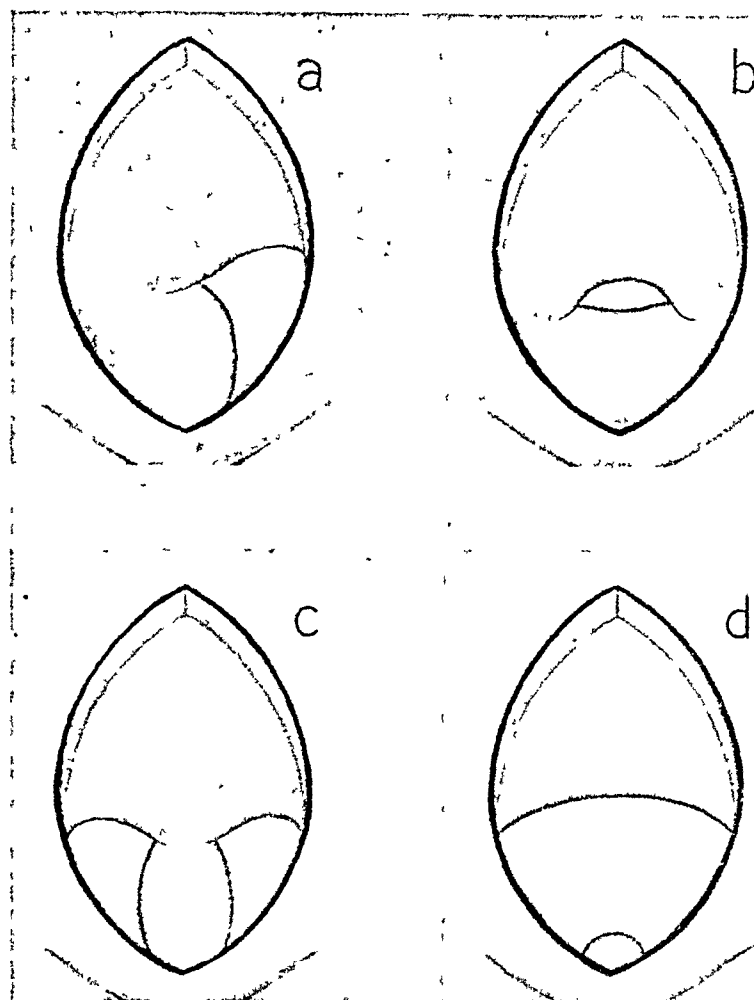


Fig. 1.—Diagrammatic representation of the unilateral paravesical (a), the supravesical (b), and the bilateral paravesical (c) approaches to the lower uterine segment. d. Adequate exposure of the lower uterine segment which may be obtained using any of these approaches—the unilateral paravesical by subsequent dissection of the supravesical and opposite paravesical areas; the supravesical by subsequent dissection of both paravesical areas; the bilateral paravesical approach by subsequent dissection of the supravesical area.

and the supravesical area (the supravesical approach). Ultimately, in complete dissections, the supravesical area and both paravesical spaces are dissected out, the bladder lies almost entirely free except for its basal attachments, and final exposure of the lower uterine segment is the same.

The paravesical approach exemplified by the Latzko technique (Fig. 4a) provided inadequate unilateral exposure which jeopardized the peritoneum, bladder, and ureter. An incomplete operation at best, it offered for several

bladder fascia and muscularis. In the second place, variations in the character of subserous peritoneum and perivesical fascia may result in such close apposition of serous peritoneum and bladder muscularis that dissection within the layers of the perivesical fascia is impossible. In the third place, proponents of

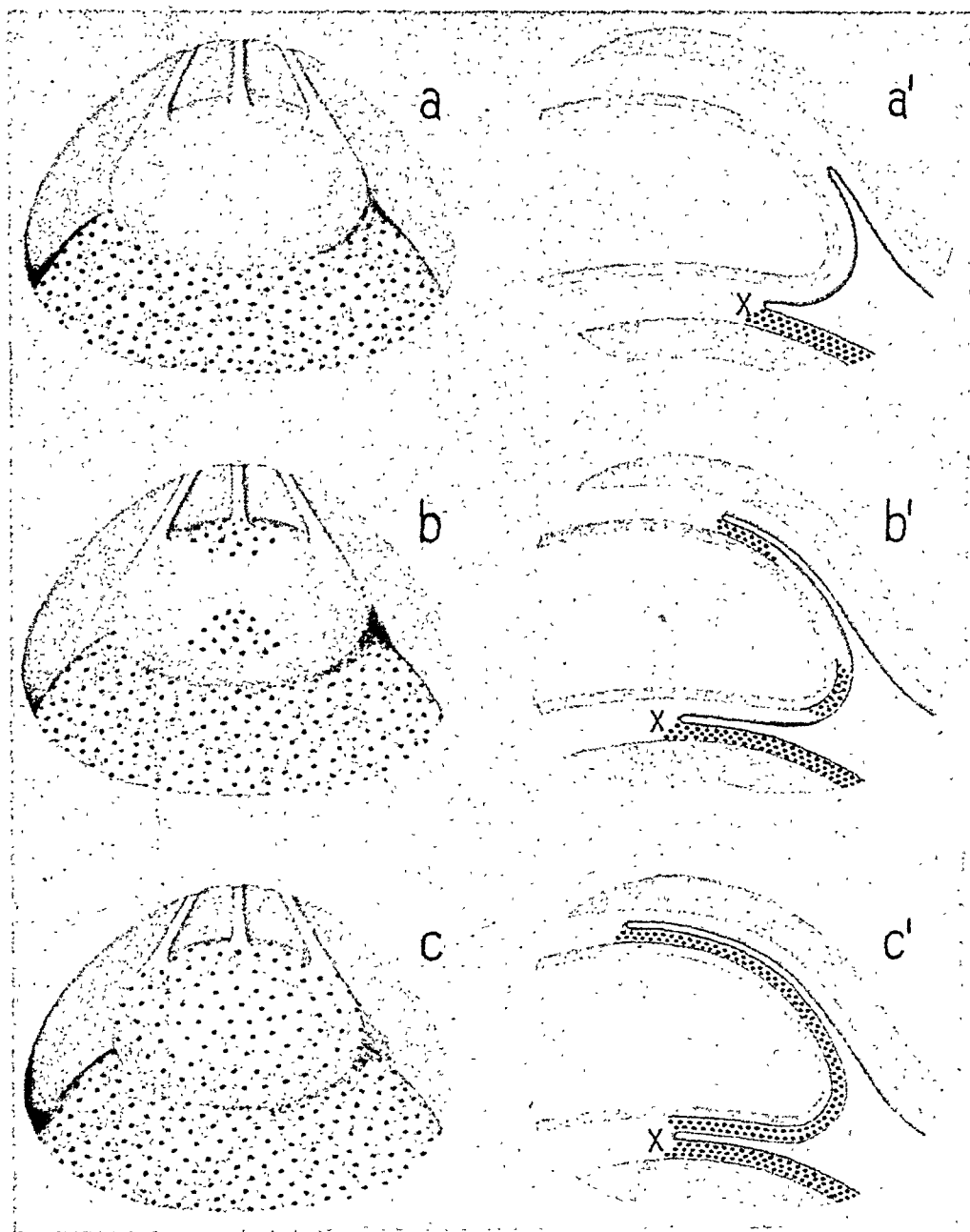


Fig. 3.—Variations in adherence of serous peritoneum to vesical fascia and muscularis. Stippling indicates adherent areas. *a* and *a'*: Abundant areolar tissue in subserous peritoneum and complete lack of adherence between serous peritoneum and vesical fascia. *b* and *b'*: Moderate areolar tissue in subserous peritoneum and small area of adherence between serous peritoneum and vesical fascia. *c* and *c'*: Minimal areolar tissue in subserous peritoneum and extensive area of adherence between serous peritoneum and vesical fascia. Note the constant area of adherence between peritoneum and uterine fascia. "x" is the constant area of areolar tissue just inferior to the uterovesical peritoneum.

these cleavage planes (within the perivesical fascia, or deeper) refer to the hernialike peritoneal sac followed during dissection. It is obvious that dissection revealing the peritoneum as a hernialike sac is carried out, for the most part, within the fibroareolar component of the peritoneum and not within the fascial or muscular coverings of the bladder.

section of the peritoneum from the bladder in the supravescical area and finally from the lower uterine segment, has proved the most reliable procedure. It takes advantage of the more constant anatomic relationships in attacking the paravesical and retrovesical dissections first; it defers dissection in the usually adherent supravescical area until the best possible control over the structures involved has been obtained.

Operative Technique

1. *Preparation of the Patient.*—With the patient anesthetized and in lithotomy position, the vulva and vagina are prepared with antiseptics, the obstetric condition of the cervix and the presenting part are determined. A Malecot catheter attached to a suitable apparatus for distending and emptying the bladder is introduced into that organ and tested. The abdomen is prepared, the patient is placed in moderate Trendelenburg position and sterile drapes arranged.

2. *Incision of the Anterior Abdominal Wall.*—The bladder having been filled with 150 to 250 c.c. of sterile water or saline solution, a midline incision is made from the symphysis pubis to the upper pole of the distended bladder. The incision is carried to the rectus sheath, hemostasis is attended to and skin towels are clipped in place. The rectus sheath is incised in the midline and both recti muscles dissected out.

A midline incision offers the following advantages: 1. it avoids the deep epigastric vessels; 2. it permits equal access to both sides of the pelvis; 3. it permits approximation of the recti muscles when closing the abdomen, a matter of some importance to gravidas with potential or actual diastasis recti; 4. it is complementary to the midline incision of prior or subsequent gynecologic surgery; and 5. with the exception of the Pfannenstiell incision, which we occasionally use, it produces the most elegant cosmetic result.

3. *The Paravesical Dissections.*—By blunt dissection, the transversalis fascia covering the distended bladder is separated laterally on one side from the posterior surfaces of the recti muscles to the yellow chicken fat in the paravesical space just lateral to the junction of the periuterine and perivesical fascias. During this dissection, the transversalis fascia diffuses into the areolar connective tissue of the paravesical space. The same procedure is carried out on the opposite side of the distended bladder.

If the peritoneal staining technique is used, the bladder is emptied at this point, the peritoneofascial flap is stained, and the bladder refilled.

At a point below the parietovesical peritoneal reflection, a short transverse incision is made through transversalis fascia and the outer layers of perivesical fascia (Fig. 5a); this incision is discontinued as the vesical veins come into view.

If the staining technique is used, the incision is made about 2 cm. below the stained parietovesical peritoneal fold; otherwise, the incision must be well down on the bladder to avoid opening the peritoneum.

By blunt dissection, the cleavage plane within the perivesical fascia is developed laterally to the point of junction of the periuterine and perivesical fascias (Fig. 5). This point will be medial to the yellow chicken fat previously identified. The layer of fascias (transversalis and outer perivesical fascias) thus isolated will contain a low-lying paravesical peritoneal reflection; the fascia is divided below the reflection (Fig. 5c and 5d). The paravesical peritoneum is wiped upward as far as possible (Fig. 5e). This completes the paravesical dissection on one side; it is repeated on the other side and the bladder emptied.

4. *The Retrovesical Dissection.*—The bladder is maintained in its collapsed state for the remainder of the operation (Fig. 6a). With the palpable collapsed bladder retracted medially by a finger and the parietes retracted laterally with a Richardson retractor, the fibroareolar connective tissue overlying the lower

decades the only practicable route to the lower uterine segment. During this period, extraperitoneal cesarean section was infrequently attempted and then only as a last resort.

The paravesical operation described by Irwin completes the Latzko procedure by dissecting over the dome of the bladder and clearing the opposite paravesical space. Satisfactory exposure of the lower uterine segment results.

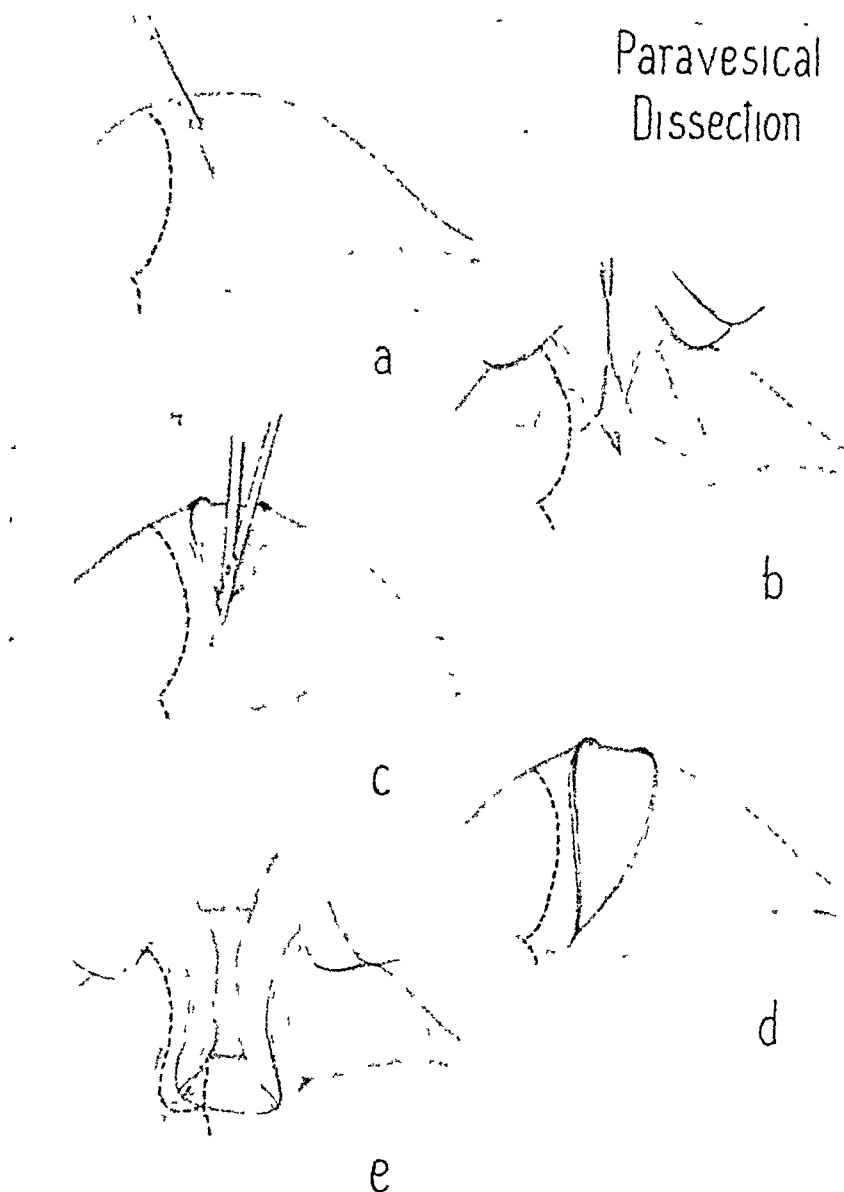


Fig. 5.—The paravesical dissection. The distended bladder and its overlying transversalis fascia have been separated by blunt dissection from the anterior abdominal and lateral pelvic walls to the chicken fat area in the paravesical space on both sides. *a*: Incision of the transversalis and outer layers of perivesical fascia below the anterior peritoneofascial fold. *b*, *c*, *d*, and *e*: Extension of this plane of cleavage within the paravesical fascia to the medial aspect of the paravesical space. This dissection is then repeated on the opposite side.

The supravescical approach (Fig. 4b) advocated by Waters exhibits initial dissection of the supravescical area with subsequent clearing of both paravesical spaces. Its technical disadvantage lies in the primary attack on the supravescical area which usually presents the most difficult dissection.

In our experience, a bilateral paravesical dissection (Fig. 4c) followed by retrovesical separation of the bladder from the lower uterine segment, with dis-

5. *The Supravesical Dissection.*—Since anatomic variations in the supravesical area are marked, its dissection can be surprisingly easy or discouragingly difficult. When abundant areolar and little fibrous tissue connect serous peritoneum and bladder fascia, separation of these structures is readily accomplished by transverse division of the entire intervening fibroareolar tissue mass (Fig. 7a).

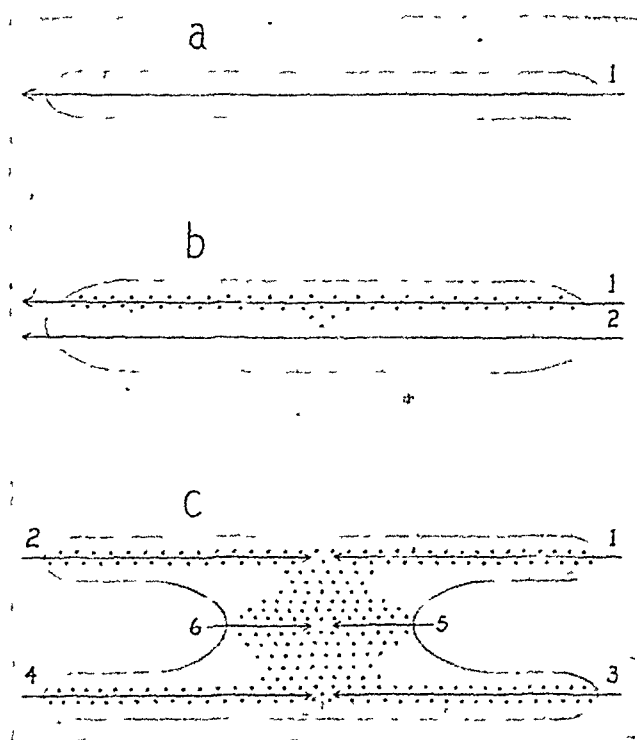


Fig. 7.—The supravesical dissection: plans of attack. Diagram of more common plans of attack on the supravesical area. Stippling indicates areas of adherence. *a*: The case with abundant areolar subserous peritoneum and no adherence of serous peritoneum to vesical fascia. *b*: The case with adherence of serous peritoneum to perivesical fascia along the anterior transverse peritoneofascial fold. *c*: The common and usually difficult case with no areolar subserous peritoneum and extensive adherence of serous peritoneum to vesical fascia in the supravesical area and along both anterior and posterior transverse peritoneofascial folds.

When serous peritoneum and perivesical fascia or bladder muscularis are intimately coapted by virtue of almost complete absence of subserous fibroareolar peritoneum and exceptional thinness of the perivesical fascia, an orderly plan of dissection is of value. Most individuals present areas of adherence along the anterior transverse fold and in the supravesical area. If adherence is slight, it may be possible to divide these structures and then the posterior transverse fold in turn from side to side (Fig. 7b). When adherence is marked, however, it is safest to dissect each structure individually from its lateral aspect toward the midline where the most intimate coaptation may be expected (Fig. 7c). Thus, dissection of the central supravesical area which includes the urachus is usually the last step in separation of the peritoneum from the bladder.

There are several maneuvers which are helpful in performing the supravesical dissection. When the retrovesical dissection has been accomplished, traction with the finger tips introduced in a medial direction behind the anterior transverse fold brings that structure into relief and facilitates its dissection (Fig. 8a). Occasionally the anterior transverse fold can be easily divided from one side to the other by sharp dissection (Fig. 8b). Rotation of the bladder and attached peritoneum through approximately 180° with sharp dissection of

uterine segment is frayed with Metzenbaum scissors at a point below the uterovesical peritoneal reflection until the glistening purplish-tinged layers of the periuterine fascia are exposed (Fig. 6b). This procedure is repeated on the opposite side of the bladder.

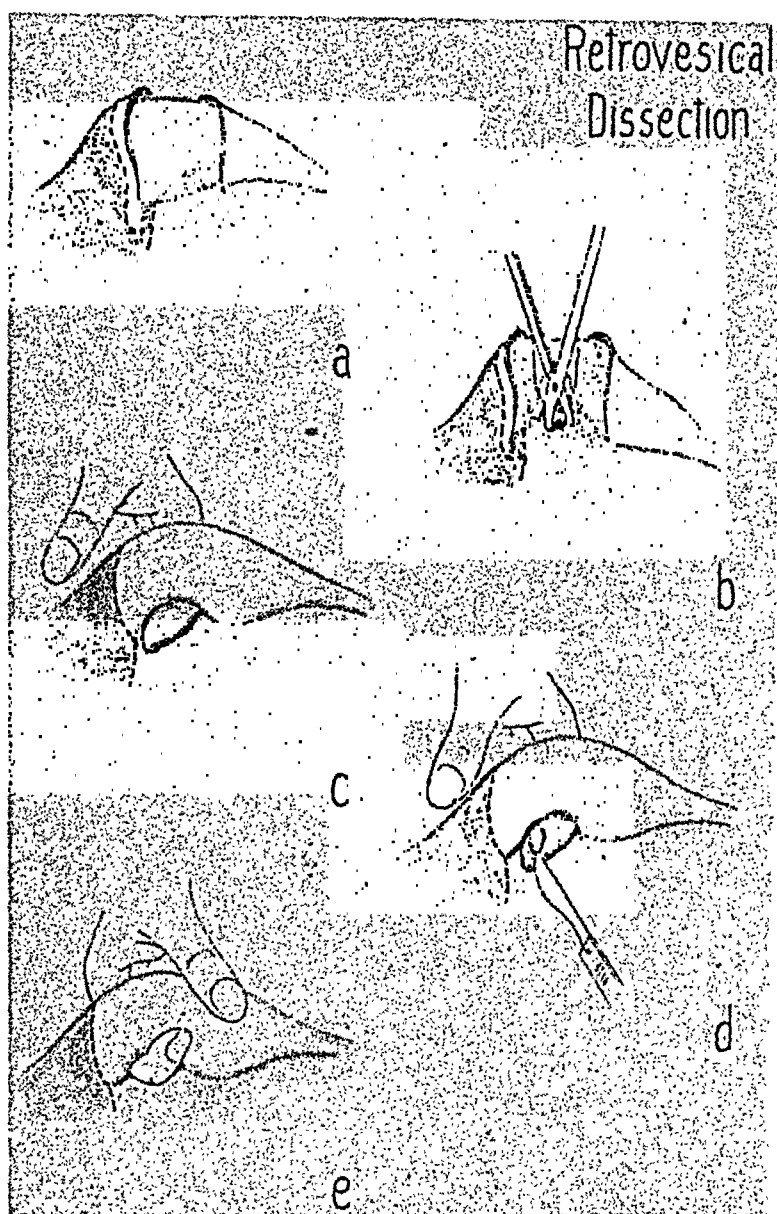


Fig. 6.—The retrovesical dissection. *a*: The collapsed bladder. *b*: With the bladder retracted medially by a finger, the fascias over the lower uterine segment are frayed until the glistening purplish-tinged uterine fascia is exposed. This step is repeated on the opposite side. *c*: The index finger inserted retrovesically between uterine and vesical fascias (in the areolar connective tissue region inferior to the uterovesical peritoneum) from one paravesical space to the other. *d*: Incision of residual fascia over the tip of the retrovesical finger, thus connecting the two paravesical spaces retrovesically. *e*: The collapsed bladder raised from the lower uterine segment.

A finger can then be introduced between the easily separated layers of perivesical and periuterine fascia from one side to the other (Fig. 6c) and the two paravesical spaces made continuous retrovesically by sharp dissection of the remaining tissues over the finger tip (Fig. 6d). The bladder can now be raised from the lower uterine segment (Fig. 6e); it is attached to peritoneum only at its supravescical area.

a fibrous cord, it is divided between ligatures of fine chromic gut (Fig. 8f). In some cases it may be necessary to separate the visible serous peritoneum from an exceedingly thin adherent perivesical fascia and bladder muscularis by dissecting in the outer layers of vesical muscularis; in easier dissections this is necessary in only a small area about the urachus, but in more difficult ones such dissection may be required over an extensive area.

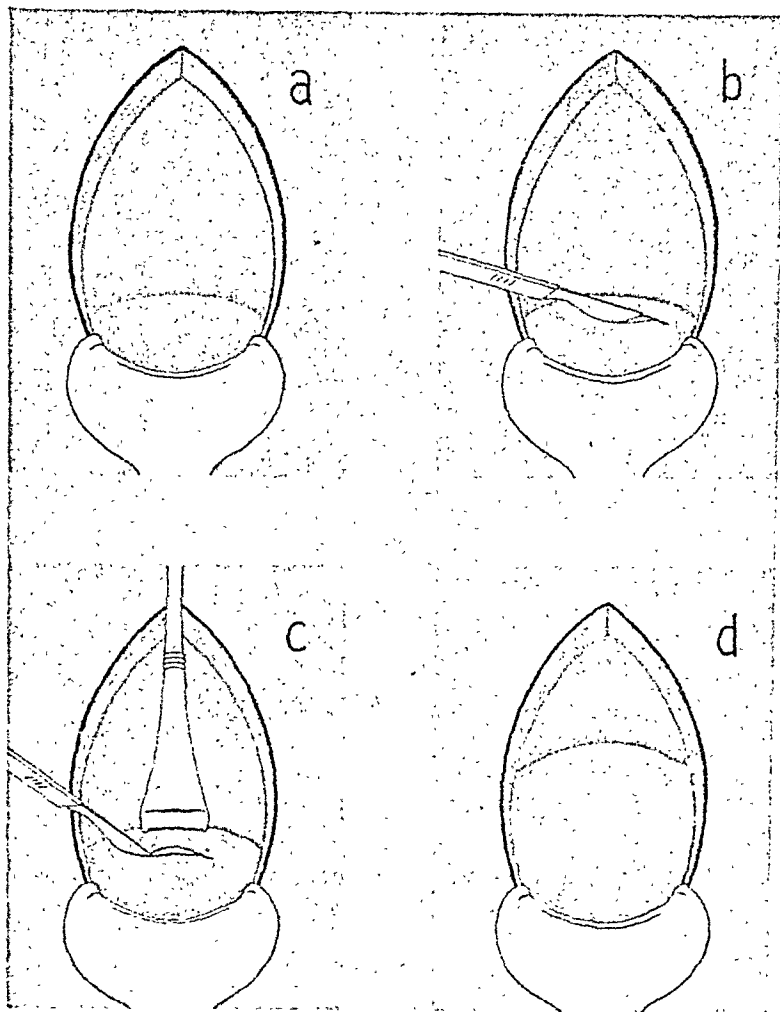


Fig. 9.—Exposing the lower uterine segment. *a*: The bladder has been placed under the symphysis behind a Doyen retractor. *b*: Incising the uterine fascia below the peritoneofascial flap. *c*: Further incision of the uterine fascia, allowing the peritoneofascial flap to be raised with a Richardson retractor. *d*: Final exposure of the lower uterine segment.

When the peritoneofascial flap has been separated from the bladder, it lies adherent to the lower uterine segment in a transverse manner (Fig. 9a). The periuterine fascia inferior to the fold is incised transversely (Fig. 9b) and the edge of a Richardson retractor introduced under the superior leaf of the dissected fascia. Upward traction places the fascia on tension, and by sharp and blunt dissection within the layers of the periuterine fascia (Fig. 9c) the fold may be elevated to give the desired exposure (Fig. 9d). This step completes that portion of the dissection peculiar to the extraperitoneal type of cesarean.

6. *Evacuation and Repair of the Uterus.*—The empty bladder is placed behind the symphysis pubis, the peritoneofascial flap is elevated by an assistant with moist gauze, and, with lateral retractors giving the necessary exposure, a low transverse cervical incision is made in the uterus.

the posterior transverse fold from the bladder is a useful maneuver in difficult dissections (Fig. 8c). At times, a finger can be gently forced between bladder and peritoneum so as to expose and facilitate division of the connecting fascia (Fig. 8d). At any point, dissection may usually be accelerated by traction on

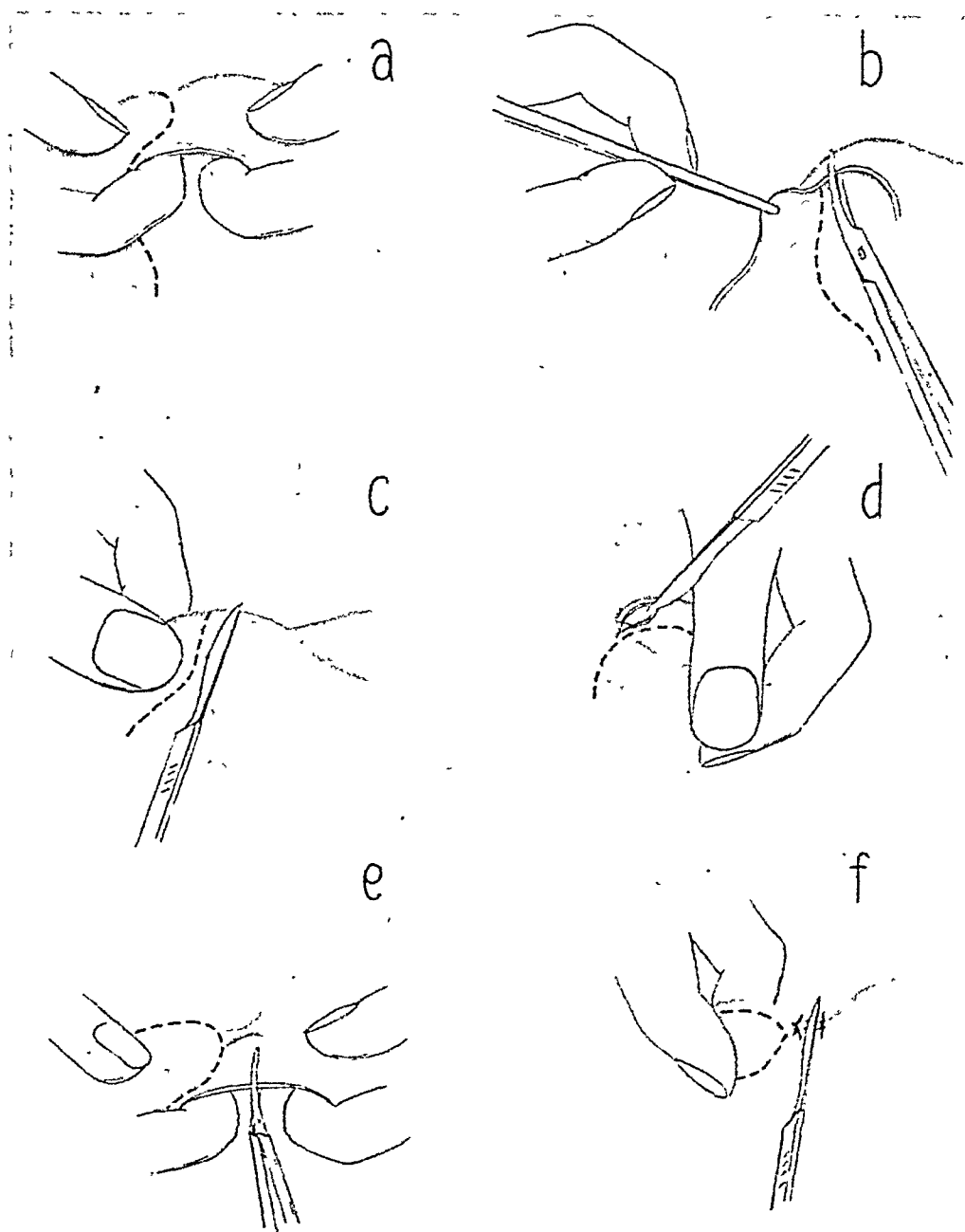


Fig. 8.—The supravescical dissection: methods. Maneuvers useful for the supravescical dissection. *a*: Exposure of the anterior transverse peritoneofascial fold by traction on the bladder and the peritoneofascial flap. *b*: Sharp dissection of the anterior transverse fold from the bladder. *c*: Rotation of the bladder to bring its posterior surface into view; sharp dissection of the posterior transverse peritoneofascial fold from the bladder. *d*: Sharp dissection over finger tip of the fibroareolar tissue between bladder and peritoneum. *e*: Dissection of fascia in supravescical area approaching the urachus. *f*: Division of the urachus between ligatures.

the bladder and the peritoneofascial flap which accentuates the joining fascia (Fig. 8e). Final separation of the bladder from the peritoneofascial flap is frequently accomplished by division of the urachus; if the urachus is more than

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The merits of the *low transverse cervical* incision originally proposed by one of us¹⁰ are: (1) it lies in the course of the majority of the cervical fibers; (2) the incision is placed in the noncontractile portion of the uterus where healing is not interfered with by postpartum contractions; and (3) the incidence of rupture during subsequent pregnancies is minimal.

After an ampule of Ergotrate has been given intravenously, the infant is delivered by suitable means (manually, by vectis, or by forceps). The cord is divided and the placenta expressed. In relatively clean cases, the placenta is removed manually. The angles of the uterine incision and its midpoints are grasped with Allis forceps and the uterine cavity inspected for residual membranes which are removed if present. The patency of the cervical canal is tested to insure lochial drainage and the glove or instrument used for this purpose discarded.

The myometrium and fascia are approximated with interrupted sutures of No. 1 chromic gut, the angle and midpoint sutures being introduced first and held with clamps to facilitate insertion of the remaining sutures. The peritoneal fascia is infolded over the first line of suture by a continuous Cushing or Lembert suture of No. 1 chromic gut.

7. *Closure of the Abdomen.*—The operative site is sponged free of blood and blood clots; there is seldom any ooze requiring attention. The bladder may be distended at this point to prove its integrity. A rubber tissue drain is placed in the retrovesical space and brought out through the lower angle of the abdominal incision. The recti muscles are loosely approximated with interrupted sutures of No. 00 chromic gut; the rectus fascia is approximated with interrupted sutures of No. 0 chromic gut; the superficial fascia is approximated with interrupted sutures of No. 000 plain gut; the skin edges are approximated with a nonabsorbable suture and the drain is fixed to the skin edge with a single suture. A sterile dressing is applied, the contractile state of the uterus is ascertained and clots are expressed from the vagina.

Summary

1. The surgical anatomy of extraperitoneal cesarean section, based on the study of forty-nine extraperitoneal operations of all major types, is presented from four interlocking points of view: (1) anatomic description, (2) planes of dissection, (3) anatomic approaches to the lower uterine segment, and (4) the technique developed from consideration of the foregoing.

2. Variations in configuration and levels of attachment of peritoneum to bladder, in the nature of the fibroareolar component of the peritoneum, in adherence of serous peritoneum to perivesical fascia, and in substance of the perivesical fascia are described. Anatomic variations of the supravescical area are emphasized. The paravesical space is described.

3. Proposed and actual planes of dissection are discussed. It is pointed out that extraperitoneal cesarean section is usually performed successfully only by employing several planes of dissection.

4. The anatomic approaches to the lower uterine segment are briefly discussed.

5. The operative technique developed as a result of the foregoing material is outlined. It consists essentially of a bilateral paravesical approach with retrovesical separation of the bladder from the lower uterine segment and subsequent dissection of the supravescical area. The easiest planes of dissection are utilized throughout.

Experimental Critique and Evaluation of Various Theories

A. A Vasoconstrictor Substance.—One of the earliest theories advanced as to the chemical nature of menstrual poison was that of Labhardt and Hussy⁸ who, on the basis of some experimental work, claimed the presence of a substance possessing vasoconstricting properties in menstrual blood. Vasoconstricting properties of normal blood serum have been described by physiologists before,⁹ but in menstrual blood the authors claimed the vasoconstricting properties were greater. Could that be due to a substance in menstrual blood closely related to epinephrine? The present writer investigated the effect of adding small quantities of epinephrine to blood serum. It was shown by him that epinephrine, in contrast to ephedrine which is sometimes called vegetable-epinephrine, in saline solutions, is quite toxic for plants, but when mixed with one per cent of blood serum the weakest concentrations to which lupine roots respond were one to fifty thousand. This is much greater than the normal amount of epinephrine present in shed blood. Furthermore, it is well known that Adrenalin is such an unstable substance that, at the pH of the blood, it is rapidly oxidized. Menstrual blood, however, retains its toxicity for many days even at room temperature. These experiments, therefore, excluded the likelihood of menotoxin being related chemically to epinephrine.

B. Another hypothesis as to the nature of menotoxin was that advanced by Sieburg and Patschke,¹⁰ Klaus,¹¹ and others. These writers thought that menstrual poison is closely related to choline. They did not, however, isolate menotoxin in chemical form and identify it with choline. On the other hand, phytopharmacologic experiments performed by Macht revealed that neither choline nor acetylcholine are toxic for lupine seedlings. It is, therefore, not probable that menotoxin is in any way related to choline chemically. We must not, however, confuse the term choline with that of cholic acid and its salts. They are not at all related to choline, but are chemically closely related to the bile acids. The latter have been shown by the present writer long ago to be very toxic for plants and the significance of that will be discussed later.¹²

C. Macaggi and Sivori¹³ regarded menotoxin as closely related to thyroxin or the active principle of the thyroid gland. The present author made experiments with thyroxin solutions on the growth of lupinus seedlings and did not find it toxic for these plants in concentrations which were even greater than those present in most clinical cases of thyrotoxicosis.

D. More recently, Steinert and Papp¹⁴ attributed the toxicity of human milk during menstruation to a reduced content in diastatic ferments. In other words, they tried to correlate menotoxin with diastase. The present writer made experiments on the growth of seedlings in diastatic solutions in different proportions, both in saline solution and in combination with blood serum, and did not find any toxic effects produced on the growth of the seedlings, even by quite concentrated solutions of that enzyme.

E. Another hypothesis is advanced by Ashley Montagu.¹⁵ He holds that menstrual toxin is identical with di-methyl-amine, a compound described long ago by Michin. We have secured specimens of pure di-methyl-amine and studied carefully the effect of those solutions on the growth of lupinus seedlings. No toxic effects were noted, even with very concentrated solutions. It appears, therefore, that di-methyl-amine is also not likely to be the active toxic agent of menstrual blood.

F. A very interesting contribution is that of Heinrich Guthmann and K. H. Henrich.¹⁶ These authors computed the amount of arsenic found in venous blood during normal conditions and during menstruation. They found that normal venous blood contains 103 gamma per cent of As. On the other hand,

CONCERNING THE CHEMICAL NATURE OF MENSTRUAL TOXIN

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TWENTY-FIVE years ago, the present writer began the development of a new branch of pharmacology to which the name of phytopharmacology was given. By this is meant the study of physiologic effects of drugs and chemicals of every sort by the use of living plant-physiologic test objects. The methods employed in such work have been extensively described in previous papers.^{1, 2, 5} Suffice it for the present purposes to call attention to the fact that this phytopharmacologic approach was found to be very useful in detecting and studying the various properties of chemicals contained in the blood.⁴ One of the first and most interesting studies conducted in this manner was the first quantitative and experimentally reliable investigation of the so-called poison of menstruation.

An elaborate monograph on the subject was published in 1924 by the present author and Miss Dorothy Lubin,⁵ in which paper it was demonstrated that a toxic substance is present in the blood, sweat, milk, and other secretions of menstrual women which can be specifically and strikingly detected by phytopharmacologic methods. Ten years later, in the paper by Macht and Davis,⁶ further studies on the subject were reported and described. Another ten years later the writer wrote a third and even more comprehensive paper⁷ dealing with both the historical and experimental studies on menstrual toxin by himself and other workers and containing an extensive bibliography on the subject. It was shown that menotoxin can produce definite pharmacologic effects on suitable zoological test objects, but, nevertheless, the phytopharmacologic approach was the most striking and sensitive one for studying this particular toxin. Even in the first paper by the author and Miss Lubin, the chemical nature of menotoxin was discussed and the authors stated that it is related to cholesterol and was probably some form of oxysterol. In the intervening twenty-five years between the beginning of these studies and the present time, menstrual toxin has been studied by various authors and different hypotheses as well as speculations have been advanced as to the chemical nature of this substance. It is the purpose of the present paper to examine the validity of these hypotheses and also to present experimental and chemical data of our own pointing to the chemistry of menstrual poison.

Method of Study

The various hypotheses advanced by different authors as to the chemical nature of menstrual toxin were put to test in two ways. In the first place, the different chemical compounds claimed to be menotoxin were tested by phytopharmacologic methods. This is an extremely useful procedure because only a very limited number of blood sera are toxic for the growth of *Lupinus albus* seedlings and, for this reason, any substance claimed to be menotoxin in nature can be conveniently put to a test by phytopharmacologic examination. A second method employs an entirely new approach to the study of the subject and involves biophysical methods which will be described later in this paper.

follows: The dry seeds of *Lupinus albus* large variety were soaked overnight in tap water at the ordinary room temperature. On the following day, the swollen seeds were planted with the hilum downward in finely ground moist Sphagnum moss containing the proper amount of moisture. The seeds were then placed in the dark and kept at a constant temperature of about 20° C. On the third day after planting the seeds, the seedlings are of convenient size, the length of the roots being generally from 20 to 30 mm. The length of these roots can be accurately measured because of a definite line of demarcation indicating the border line between root and stem. After recording the exact length of a root, the seedling is placed in an upright test tube of hard glass containing a nutrient solution for plants, the seed resting on the upper edge of the tube. The solution employed was the so-called Shive²³ solution which contains calcium nitrate, magnesium sulphate, and monopotassium acid phosphate. Such a solution is prepared by mixing 10.4 c.c. of a 0.5 molar solution of calcium nitrate, 30 c.c. of a 0.5 molar solution of magnesium sulphate, and 36 c.c. of a 0.5 monopotassium phosphate solution, with distilled water sufficient to make 1 liter. The normal growth of the lupine rootlets was studied by immersing the seedlings in a mixture of normal Shive solution with an equal part of distilled water. The effect of unknown substances was studied by Macht and co-workers in other connections, by adding a definite percentage of the unknown to the distilled water and then mixing with an equal part of Shive.

In the present work, the normal growth of the seedlings was first determined by using equal parts of distilled water and the Shive solution.²³ In these extensive experiments the average growth of at least twenty and often thirty seedlings was determined for each solution used.

After all the solutions have been prepared and all the seedlings have been measured and immersed in them, the plants are placed in a low-temperature thermostat and left overnight at a constant temperature of 15° C. in the dark. The temperature throughout the experiment was followed by means of a thermograph, although variations or fluctuations in the temperature were of no significant importance, inasmuch as all the plants or seedlings, including the controls, were always kept under the same conditions. After a period of twenty-four hours and sometimes twenty hours, the seedlings are examined again. The roots are measured and the growth in various solutions is compared with the average growth in normal Shive. The sharply defined straight roots are measured at the beginning and end of every experiment, and the ratio of growth of the seedling roots in the various drug solutions is expressed as a percentage of their growth in the control solution according to the formula,

$$\text{Index of Growth} = \frac{X}{N} \times 100$$

in which N represents average growth of controls and X the average growth in the drug solution. All of the seedlings were allowed to grow for twenty-four hours in the dark at 15° C.

B. Nonphytotoxic Substances.—The action of solutions of the various compounds discussed above, which have been suggested by various authors as responsible for menotoxin or the toxic effects of menstrual blood serum, is exhibited in Table I. Here are listed the concentration of the drugs studied and the phytotoxic indices in plant-physiologic saline solutions. It will be seen that all of those bodies are either not toxic at all or are no more toxic than normal blood serum.

In the same table are also shown the effect of x-ray irradiation on such solutions in respect to their phytotoxic properties. Here it will be noted that irradiation produced either no change in toxicity or actually rendered the solu-

menstrual blood is much richer in arsenic and contains about 320 gamma per cent of the element. This difference in the quantity of arsenic suggested that the toxicity of menstrual blood might be due to its greater arsenical content. However, this was not borne out by phytopharmacologic experiments. The present writer studied the effect of arsenical solutions with and without blood serum on the growth of lupinus seedling roots and found that concentrations even of four hundred to five hundred gamma per cent were not toxic for lupinus seedlings, whereas menstrual blood always is.

G. Italo Vandelli¹⁷ recently called attention to another interesting finding. Normal blood always contains small quantities of *histamine* to the amount of 0.1 gamma per cent. Menstrual blood, on the other hand, was found to be much richer in histamine, containing as much as 0.36 gamma per cent. In order to ascertain whether this might account for the phytopharmacologic properties of menstrual blood, we have made experiments with solutions of histamine much stronger than the above but found that they produced no inhibitory effect on the root growth of lupinus seedlings in hydroponic solutions containing histamine.

H. Still another interesting study worth mentioning in this place is that of Eva R. Hutzler.¹⁸ This investigator noted that menstruation produced a depressant effect on the excretion of *ascorbic acid* or vitamin C after ingestion of certain fruit. Could an excessive retention of ascorbic acid in the blood account for the toxic properties of menstrual blood? This was investigated by the present writer some years ago and studied on a large number of plants, the results of which study were analyzed statistically. It was found that ascorbic acid or vitamin C in aqueous solutions did inhibit growth of lupine seedlings but only in such concentrations as could not possibly be present in menstrual blood. Similarly, mixtures of ascorbic acid with normal blood serum were not found to be phytotoxic in concentrations greater than vitamin C occurs in menstrual blood. We may, therefore, conclude that ascorbic acid probably has no relation of chemical nature to menotoxin.

I. Finally, we wish to mention the most recent and elaborate studies by Smith¹⁹ of Boston on a body which he called *necrosine*. This substance or mixture of substances was first described by Menkin,²⁰ and Smith employed his method in producing it among dogs. He claimed, for some reason not quite clear to the present writer, that menotoxin is identical with or closely related to necrosine. It was, therefore, very interesting to investigate the influence of necrosine on growth of plants. The present writer produced necrosine in dogs by the Menkin method and studied the effect of its solutions on the growth of lupine seedlings. It was found that in no case did necrosine inhibit the growth of the seedlings or produce any toxic effect. The conclusion based on phytopharmacologic studies, therefore, is that neither necrosine nor any other chemicals mentioned above agree with the properties of menstrual toxin which are exhibited by phytopharmacologic methods.

Experimental Data

A. *Method*.—The experimental data briefly mentioned in the above critique of various hypotheses as to the nature of menstrual toxin, and revealing their inadequacy, may now be presented in more concrete form.

The technique employed in the present author's phytopharmacologic work has been described in great detail in other papers.^{21, 22} Briefly, it is performed as follows:

The toxicity of the various preparations was studied on growth of the seedlings of *Lupinus albus* by measuring carefully the elongation of the well-defined single, straight rootlets. The *Lupinus albus* is especially adapted to experiments in plant physiology and pharmacology because it can be easily germinated and the growth of the roots accurately measured. The procedure employed was as

bloods. It was actually possible to distinguish between blood stains on cotton or linen fabric made by normal and menstrual bloods, respectively.²⁴ Menotoxin is not destroyed by mild acids or alkalis. It does not pass, however, through dialyzing membranes. It is soluble in alcohol, chloroform, ether, and acetone. These various chemical properties of the toxin, together with numerous pharmacologic tests produced both on animal and vegetable living tissues led the authors to suspect a close relationship between menotoxin and cholesterol or more strictly speaking, oxycholesterin.

Thus, it was discovered that wherever found in the human body, whether in the skin fat or in the vernix caseosa or elsewhere, even weak solutions of oxycholesterin in plant-physiologic media markedly inhibited the growth of *Lupinus albus* seedlings. Unna and Golodetz²⁵ have shown that the human skin is rich in fats containing considerable quantities of cholesterol and cholesterol derivatives. Furthermore, comedones and sebaceous glands of the face, and fingernails have proved to be rich in cholesterol derivatives. Phytopharmacologic experiments performed by the writer revealed that extracts of all these were toxic for *Lupinus albus* seedlings. Other poisons of animal origin, such as the toad poison, *bufagin*, of Abel and Macht,²⁶ had been found by the latter to be very poisonous for plant growth. This toad poison, as well as others later studied by Chen,²⁷ are all derivatives of cholesterol. Perhaps the most striking single experimental proof supporting the original oxycholesterol theory was the finding by Rahn,²⁸ Barnes,²⁹ Ferguson,³⁰ and Christiansen³¹ that inhibitory effects on yeast similar to those the first writer had observed in his radiologic tests on menstruating women were produced by cholesterol itself. Further support is lent the cholesterol or oxycholesterol hypothesis by the fact that recent chemical studies on the structure of the sex hormones in general and of ovarian hormones in particular have disclosed their intimate relationship in chemical structure to cholesterol. The findings made by Macht and his associates on the interrelation of menotoxin and bile salts also support this view.

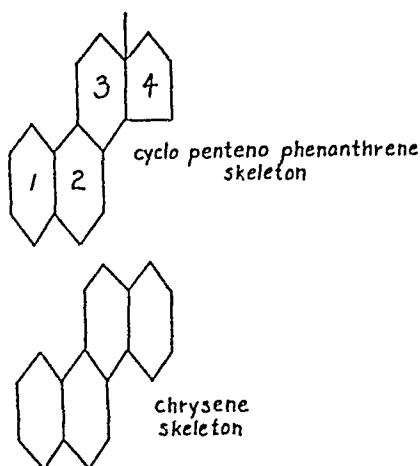


Fig. 1.—Skeletons of the chemical structure of the principal steroids.

Inasmuch as it is now known that all of the sex hormones, both male and female, belong to the steroid group of chemicals, it was deemed worth while to investigate, as far as possible, the action of solutions of ovarian hormones on the growth of plants. Special studies were made by the present author on the effects of estrone and progesterone on the root growth of *Lupinus albus* seedlings

tions of the drugs less phytotoxic. All of these radiations were made with a Westinghouse Duocondex x-ray machine at the Sinai Hospital, Baltimore, operated on 200 kv. and a current of 20 Ma. and target distance of 50 cm., employing a composite filter of 1 mm. Al and 2 mm. Cu. The author is indebted to Dr. Marcus Ostro for his courtesies in using the above machine. The significance of these findings will be explained further on.

TABLE I. ROOT-GROWTH OF LUPINUS ALBUS SEEDLINGS IN SOLUTIONS OF SOME SUSPECTED COMPOUNDS

DRUG	CONCENTRATION	MANNER OF TREATMENT	PHYTOTOXIC INDEX IN SHIVE (PER CENT)
Choline	1:500	Untreated	97
	1:500	X-rayed with 180 r	99
Di-methyl-amine	1:25,000	Untreated	100
	1:10,000	Untreated	96
Histamine	1:5,000	Untreated	81
	1:5,000	X-rayed with 180 r	94
Thyroxin-l	1:2,000	Untreated	79
	1:2,000	X-rayed with 180 r	70
Thyroxin-d	1:2,000	Untreated	90
	1:2,000	X-rayed with 180 r	99
Arsenic	1:100,000 As	Untreated	70
(Fowler's Sol.)	1:200,000 As	Untreated	85
Diastase	1:1,000	Untreated	75
	1:2,000	Untreated	90
Necrosin	24 hours serum 1 per cent	Untreated	94
	48 hours serum 1 per cent	Untreated	62
Ascorbic acid	1:50,000	Untreated	70
Epinephrine HCl	1:40,000	Untreated	73

In Table II are given the statistical data of an experiment with ascorbic acid or vitamin C which illustrates well the reliability of phytopharmacologic experimentation when performed by a carefully trained and experienced pharmacologist acquainted with plant-physiologic methods.

TABLE II. STATISTICAL EXPERIMENT WITH ASCORBIC ACID

GROWTH OF LUPINUS SEEDLINGS IN SOLUTIONS 1:50,000			
Controls in Normal Shive Solution		Seedlings grown in vitamin C solution	
= 100 seedlings		1:50,000 = 100 seedlings in Shive	
Average growth of roots in 24 hours		Average growth of roots in 24 hours	
at 15° C. = 12.2 mm.		at 15° C. = 8.5 mm.	
		Phytotoxic Index = 70 per cent	
Standard Deviation	= 2.18	Standard Deviation	= 2.49
Probable Error PE	= 0.208	Probable Error PE	= 0.237

$$PE \text{ diff} = PE (\text{control}) + PE (\text{vitamin C}) = 0.315$$

$$\text{Validity or Critical Ratio} = \frac{D}{PE \text{ diff}} = 11.7$$

Concerning the Relationship of Menotoxin to Cholesterol

Even in the earlier monograph of Macht and Lubin some of the physical and chemical properties of menotoxin were described by those authors. It was shown that exposure to heat does not change the toxicity of menstrual blood serum. Neither do drying and freezing destroy the phytotoxic properties of such

Biophysical Evidence

Mention has already been made by the author that the phytotoxic properties of menstrual toxin can be readily distinguished from those of pernicious anemia by their response to ultraviolet rays.³⁴ It was found that short exposures of pernicious anemia serum to the rays of a mercury vapor lamp were followed by a complete loss of toxicity. On the other hand, when menstrual serum was exposed to such rays, no change in toxicity occurred and occasionally the serum became even more phytotoxic.

In the past few years, Macht and Ostro, experimenting on the pharmacologic effects of x-rays, discovered that exposure of pernicious anemia serum, the serum of pemphigus, and the sera from various psychotic patients were rapidly detoxified or rendered less phytotoxic by irradiation with short x-rays filtered through a composite filter of 1 mm. Al and 2 mm. Cu. To their surprise, it was found that when menstrual serum was exposed to the same rays the phytotoxic properties were not destroyed by 100 r. or more and, in fact, they were usually enhanced. Table IV illustrates such findings made in twelve experiments.

This interesting discovery suggested an examination of other steroid compounds in respect to their phytotoxic properties before and after exposure to short or hard x-rays. A considerable number of such compounds were collected and examined. Most of these are quite insoluble in water but fortunately they are soluble in sufficient amounts to exert phytopharmacologic effects. Table V gives a list of the compounds examined and also their toxicity for the root growth of *Lupinus albus* seedlings before and after irradiation with roentgen rays. Table VI shows how even very weak solutions of estrone and progesterone are rendered more toxic by irradiation. It will be noted that, in every case, the irradiated specimens were much more phytotoxic than the nonirradiated ones. It is interesting to note also that this group of steroids include important substances belonging to diverse pharmacologic groups. Thus, it includes various cardiac glucosides; it includes some of the best-known vitamins, such as ergosterol and calciferol; it includes the toad poisons; and finally, it includes the large group of sex hormones which have already been isolated in pure chemical form up to the present time. The general structure of these steroid compounds is shown in Fig. 1. They are all related to phenanthrene or chrysene and a more intimate chemical structure can be found in the valuable monograph on steroid compounds by Sobotka.³⁵ It is always dangerous to make general statements in any kind of scientific researches and especially so in pharmacologic work which aims at tracing relationships between chemical structure and physiologic action, but it is certainly remarkable to find that all of the steroid compounds so far studied by the present author in respect to their phytotoxic action are rendered more potent by roentgen irradiation. It is, therefore, perhaps, permissible to regard this remarkable pharmacologic property as a further corroboration of the author's hypothesis that menotoxin is closely allied to cholesterol on the one hand and to the sex hormones on the other hand and is chemically to be classed with the steroid group of chemical compounds which play such a very important role in biochemistry. Thus we see that, in the light of twenty-five years of experimentation and experiences since the first publication of the monograph on menotoxin by Macht and Lubin, the original contention that this toxin is closely related to the phenanthrene derivatives, cholesterol and oxycholesterol, has been largely corroborated; and, while it is a separate toxic entity, it is probably closely related to the female sex hormones which are also now known to be natural products of phenanthrene and belong structurally to the steroid class of chemical compounds.

by the methods already described above. Fortunately, these insoluble substances are sufficiently soluble in plant-physiologic saline to exert definite effects on the growth of the seedlings. Briefly, the method employed was to dissolve the hormones in strong ethyl alcohol and, using this solution as a starting point, to dilute it to very low concentrations suitable for the growth of seedlings without danger of harming the plants by the dilute alcohol. It was found that very weak solutions of estrone actually produced stimulation in the growth of the seedlings but when slightly stronger solutions were employed they were definitely phytotoxic. On the other hand, progesterone even in very extremely dilute concentrations exerted an inhibitory phytotoxic influence on the lupine seedlings.³² These effects are shown in Table III.

TABLE III. TABLE OF ROOT GROWTHS

ESTRONE - 1:200,000		PROGESTERONE - 1:200,000	
PHYTOTOXIC INDEX (PER CENT)	NO. OF ROWS	PHYTOTOXIC INDEX (PER CENT)	NO. OF ROWS
120	3	85	3
112	3	78	3
136	3	73	3
120	2	69	2
135	3	84	3
120	2	69	2
101	2	60	2
116	2	78	2
108	2	77	2
103	1	88	1
108	3	77	3
111	3	66	3
116	2	78	2
Average	117	Average	75

Recent chemical studies support this view for the findings of the present writer and his associates regarding the chemical structure of menotoxin and those of Rahn, Barnes, Ferguson and other investigators indicate its probable close relationship to oxycholesterol. It is now known that the ovarian hormones also are closely related to that substance, the investigations of Mandelshtam, Tschalkowsky, and Bondarenko³³ supplying further evidence in this connection. Studying the chemical nature of menotoxin by phytopharmacologic methods, these investigators also experimented on the effect of folliculin and the lipoid portions of the ovaries on plant growth and concluded that menstrual poison is closely related to the ovarian sex hormones. The present writer found that while crystalline estrone solution has a tendency to stimulate root growth of *Lupinus albus* seedlings, crystalline progesterone definitely inhibits it. The findings of Macht and his associates on the interrelation of menotoxin and bile salts also tend to support the view that menotoxin is closely allied to cholesterol. It is remarkable that such divergent substances as the carcinogenic chemicals, digitaloid drugs, toad poisons, sex hormones, ergosterol, calciferols and the group of compounds included under vitamin D, and menotoxin are all closely related chemically. All these are derivatives of phenanthrene and possess a structure not far removed from that of oxycholesterol. Such a relationship does not preclude the possibility of menotoxin's being much more toxic than the ovarian hormones, as pharmacology abounds in striking examples of chemicals closely related in structure yet exhibiting diametrically opposite physiologic and toxicologic properties, due to slight alterations in the relative position of some of their atoms.

Summary

1. Various theories held as to the nature of menstrual toxin have been described.

2. These have been put to test by phytopharmacologic experiments and found inconclusive.

3. All evidence gathered from the author's own experimental investigations, as well as data gathered from literature, points to menotoxin's being closely related pharmacologically and chemically to cholesterol and oxycholesterol on the one hand, and to the female sex hormones on the other; all of these compounds are natural products of phenanthrene, and belong to the important class of organic compounds known as steroids.

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TABLE IV. MENSTRUAL SERA

NO.	PHYTOTOXIC INDEX	PHYTOTOXIC INDEX AFTER RADIATION
	NONRADIATED (PER CENT)	THROUGH 1 MM. AL., 2 MM. CU., 108 R. (PER CENT)
1	60	54
2	50	57
3	50	54
4	68	69
5	47	46
6	57	49
7	52	46
8	47	44
9	48	46
10	48	48
11	48	20
12	34	19
Average: 60.9		Average: 55.2

TABLE V. STEROID DRUGS

ROOT-GROWTH OF LUPIN'S ALBU'S SEEDLINGS IN IRRADIATED AND NONIRRADIATED SOLUTION				
DRUG	CONCENTRATION	PHYTOTOXIC INDEX		
		NOT RADIATED (PER CENT)	X-RAYED THROUGH 1 MM. AL. R.	2 MM. CU. (PER CENT)
Digitoxin (Winthrop)	1:100,000 in 1% Alc Shive	81	180	77
Digitaline Nativele	1:25,000	91	180	83
Digitoxin (Wyeth)	1:100,000 in 1% Alc Shive	62	90	54
Digitoxin (Wyeth)	1:100,000 in 1% Alc Shive	62	180	47
Digitoxin (Wyeth)	1:100,000 in 1% Alc Shive	62	270	38
Lanatoside (Cedilanid)	1:100,000 in 1% Alc Shive	77	108	59
Cubain	1:50,000 in 1% Alc Shive	85	180	66
Cholesterol	Sat. Sol. in 1% Alc Shive	85	108	76
Ergosterol	Sat. Sol. in 1% Alc Shive	71	108	58
Calciferol	Sat. Sol. in 1% Alc Shive	88	180	72
Sodium cholate	1:5000	78	180	57
Testosterone	Sat. Sol. in 1% Alc Shive	80	180	68
De-hydro-iso-androsterone	Sat. Sol. in 1% Alc Shive	65	180	50
Alpha estradiol	Sat. Sol. in 1% Alc Shive	80	144	51
Pregneninolone	Sat. Sol. in 1% Alc Shive	71	180	51
Di-hydro-tachysterol	Sat. Sol. in 1% Alc Shive	68	108	42
Bufagin (B-marinus)	Sat. Sol. in 1% Alc Shive	87	144	71
Estrone (crystalline)	1:100,000 in 1% Alc Shive	98	180	75
Progesterone (crystalline)	1:100,000 in 1% Alc Shive	80	180	63

TABLE VI. ROOT-GROWTH IN ESTRONE AND PROGESTERONE

CRYSTALLINE ESTRONE		CRYSTALLINE PROGESTERONE	
SOLUTION	INDEX OF GROWTH (PER CENT)	SOLUTION	INDEX OF GROWTH (PER CENT)
Saturated aqueous solution in Shive 13 experiments, 31 rows of 10 plants each	117	Saturated aqueous solution in Shive 13 experiments, 31 rows of 10 plants each	75
Solution in 1% Alc Shive 1:100,000		Solution in 1% Alc Shive 1:100,000	
Nonradiated	98	Nonradiated	75
X-rayed 180 r.	75	X-rayed 180 r.	60

4. Stacy (1929) found 2 patients who had been treated with radium for fibroids, two and seven years previously, respectively, among 333 cases of corpus cancer at the Mayo Clinic.
5. Macfarlane (1932) added a case in which carcinoma developed in a 60-year-old woman, fifteen years after an x-ray menopause for a uterine myoma.
6. Martindale (1933) reported 2 cases of fundal carcinoma which developed seven and three years, respectively, after induction of the menopause by means of x-ray irradiation. In a third case, sarcoma was found four years after irradiation of a fibroid uterus.
7. Schmitz (1934) discovered 9 carcinomas of the uterus among a group of 433 women who had been treated previously with x-rays or radium for uterine hemorrhage resulting from benign lesions.
8. Höffmann (1934) recorded a case of fundal carcinoma which developed three years after an x-ray castration.
9. Fournier (1935) reported a case in which corpus cancer developed in a patient aged 53 years, ten years after a radiotherapeutic menopause induced by x-rays and radium.
10. Norris and Behney (1936) observed 11 pelvic carcinomas (organ not stated) among 1,006 patients who had been treated with intrauterine radium two or more years previously for functional bleeding or uterine myomas.
11. Pemberton (1936), in discussing the paper of Norris and Behney, stated that of 4 pelvic tumors which developed among 425 women who had been treated with radium two or more years before for functional bleeding, at least 1 was an endometrial cancer. This was diagnosed 11 years after the irradiation.
12. Strachan (1936) added 2 more cases. The first was that of a girl who had had 3 curettages and finally intrauterine radium (2,400 mg. hr.) at the age of 24 years, for bleeding associated with endometrial hyperplasia. Three years of amenorrhea followed. Four years later a papillary carcinoma of the endometrium was discovered. The second patient, a woman 45 years of age, was given intrauterine radium (2,400 mg. hr.) for climacteric bleeding. Four years later she was found to have carcinoma of the fundus.
13. Malpas (1937) recorded another case of corpus cancer after a radium menopause. He also cited a personal communication from Essen-Möller, who observed 6 cases of endometrial carcinoma after the same treatment and accordingly abandoned it.
14. Mazzola (1938) reported the case of a young woman who had 3 radium treatments (1,200 mg. hr. total) and 2 x-ray treatments (650 r. total) for recurrent endometrial hyperplasia over a period of nine years and was found to have an adenocarcinoma of the endometrium 3 years later.
15. Luker (1939) treated his patient, aged 51, with 1,800 mg. hr. of radium because of climacteric bleeding (curettings showed secretory endometrium). After three years' amenorrhea, she was found to have a carcinoma of the fundus.
16. McDonald, Broders, and Counseller (1940), in their study of 20 cases of sarcoma of the endometrium, found that 2 of the patients had had their menopause induced previously by radium or x-rays.
17. Costolow (1941) reported 3 patients with carcinoma of the corpus among a group of 1,009 patients treated with radiation for myoma and followed for two and one half to twelve and one half years.
18. Vogt (1941) added another case of endometrial carcinoma which developed two years after the treatment of a 59-year-old woman with 1,000 mg. hr. of radium because of a benign polyp of the endometrium.
19. Scheffey (1942), from among a total of 124 cases of fundal neoplasms, reported 13 cases, including 1 myosarcoma, in which the patients had received previous radiation therapy for presumably benign conditions. Most of the previously irradiated patients, however, probably had cancer of the uterus at the time of their original treatment.
20. Burnam (1942), in discussing Scheffey's paper, reported 6 malignant tumors of the fundus, including one sarcoma, which developed among 625 patients treated with intrauterine radium for post menopausal bleeding of benign origin.
21. Randall (1945) observed 4 cases in which adenocarcinoma of the endometrium was recognized a year or more after the patient had received 1,000 to 1,800 mg. hr. of intrauterine radium.

MALIGNANT TUMORS OF THE UTERINE FUNDUS SUBSEQUENT TO IRRADIATION FOR BENIGN PELVIC CONDITIONS

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EXPOSURE of the female genital organs to radiant energy in the form of x-rays or radium emanations may not be as innocuous as it has long been believed to be. At least 21 of the 270 patients who have been treated for malignant tumors of the uterine fundus on the gynecologic service of the Roosevelt Hospital have had previous pelvic irradiation for benign conditions. It is the purpose of this report to review these cases and to assess the possible role of radiotherapy in the subsequent development of uterine cancer.

This problem assumes practical clinical importance in view of the frequency with which many gynecologists use radium and roentgen therapy for uterine myomas and benign uterine bleeding (Norris and Behney, 1936; Crossen and Crossen, 1947; Schmitz and Towne, 1947; Lockwood, Smith, and Walker, 1947). Approximately 13 per cent of women approaching the end of their menstrual life suffer from excessive flow (Corscaden, Fertig, and Gusberg, 1946). Randall (1945) has shown that women with menorrhagia immediately preceding the menopause have a peculiar predisposition to the later development of endometrial cancer. This thesis has been extended by Corscaden, Fertig, and Gusberg, whose calculations show that 9.6 per cent of women who experience excessive bleeding at the climacteric are destined to develop cancer of the endometrium before the age of 80. This is more than 3 times the expected incidence. Werner (1925), Taylor (1932), Macfarlane (1932), and Randall (1945) have suggested that pelvic irradiation may serve as a prophylactic measure against the development of corpus cancer in such patients. Others, however, believe that radiant energy may stimulate cancer formation in the uterus. Statistical evidence is lacking to support or refute these views. It has been difficult to dissociate a possible carcinogenic effect of the rays from an inherent susceptibility which patients so treated may have to the disease.

The following is a chronological summary, probably incomplete, of the published reports of cases in which fundal cancer has developed subsequent to the treatment of women with radium or x-rays for benign pelvic conditions.*

1. Werner (1925) reported 3 cases in which carcinoma of the corpus occurred in women aged 36 to 47 years, between eight months and seven years after treatment with x-rays. These were among a total of 2,680 patients similarly treated.

2. Vogt (1926) reported 3 cases of fundal carcinoma after x-ray castration (one patient having received radium also), and 3 cases of sarcoma of the uterus after exposure to x-rays. His review of the literature, including his own patients, showed 30 cases of uterine carcinoma and 7 cases of uterine sarcoma following previous x-ray therapy.

3. Bland (1929) treated a patient, aged 56 years, with 2,400 mg. hr. of intrauterine radium for a myoma. Three years later she was found to have an early endometrial cancer.

*Forty additional cases have been reported recently by Toffe, H. H., Eckman, P. F., and Wells, A. H., *Minnesota Med.* 31: 789, 1948, and Smith, F. R., and Bowden, L.: *Am. J. Roentgenol.* 59: 796, 1948.

TABLE I. FUNDAL NEOPLASMS IN WOMEN TREATED PREVIOUSLY WITH PELVIC IRRADIATION

CASE	AGE	IRRADIATION	ORIGINAL DIAGNOSIS	INTERVAL	TUMOR TYPE
1	57	Radium: 1,500*	Hyperplasia	5 years	adenocarcinoma
2	65	Radium: ?	"Non-malignant"	4 years	adenocarcinoma
3	61	Radium: ? 2 applications	Postmenopausal bleeding	1 ½ years	adenocarcinoma
4	56	X-ray	Menorrhagia	7 years	adenocarcinoma
5	60	Radium: ?	Myoma	Unknown	adenocarcinoma
6	68	X-ray: 2 series	Unknown	10 years 5 years	adenocarcinoma
7	65	Radium: 1,000	Hyperplasia	4 years	adenocarcinoma
8	55	Radium: 1,216	Hyperplasia	19 years	adenocarcinoma
9	54	X-ray	Myoma	12 years	adenocarcinoma
10	37	Radium: 800	Hyperplasia	16 years	adenocarcinoma
11	40	Radium: ? X-ray	Myoma	8 months	adenocarcinoma
12	74	Radium: 400	Hyperplasia	5 years	adenoacanthoma
13	52	Radium: 350	Urethral caruncle	5 years	adenoacanthoma
14	56	Radium: 600	Hyperplasia	13 years	adenoacanthoma
15	52	X-ray	Myoma	7 years	myosarcoma
16	67	Radium: ? Radium: 1,200	Myoma Polyp	5 years 1 year	myosarcoma
17	54	Radium: ?	Myoma	10 years	carcinosarcoma
18	61	Radium: 1,200	"Benign"	12 ½ years	mixed tumor
19	55	Radium: ?	Myoma	14 years	mixed tumor
20	64	Radium: ?	Menopausal bleeding	9 years	mixed tumor
21	59	Radium: 1,000	Polyp	6 ½ years	not determined

*Radium dosage is expressed in milligram hours.

CASE 14.—V. M. (R. H. No. 43066), an Irish widow, 43 years of age, was admitted to the gynecologic service of the Roosevelt Hospital for the first time on Dec. 7, 1933, complaining of menopausal symptoms and of vaginal bleeding of three weeks' duration. Her pelvic organs seemed grossly normal. Curettage was performed on Dec. 9, 1933, at which time 50 mg. of radium was inserted into the uterine cavity and allowed to remain for 12 hours, giving a total dose of 600 mg. hr. Histologically, the curettings showed endometrial hyperplasia, this diagnosis being corroborated later by study of sections cut from different levels of the block. The patient remained well until March 21, 1947, 13 years later, when she was re-admitted to the hospital at age of 56 because of a bloody vaginal discharge which began one week previously. Her uterus felt boggy and about twice normal size. Curettage on March 22 yielded a large amount of necrotic tissue, sections of which showed adenoacanthoma (Fig. 1). Total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed on March 24, 1947. The uterine cavity was filled with a foul, polypoid, necrotic tumor, with extension through about half the thickness of the myometrium.

CASE 17.—D. L. (R. H. No. 24318 and No. 40187), a widowed white woman with one child, had a radium menopause induced at another hospital in 1936, at age 44, because of menorrhagia associated with uterine myomas. Re-examination of the curettings obtained at this time showed normal secretory endometrium. The dose of radium could not be determined but the patient had no further bleeding until 1940. Bleeding of varying severity then began to recur at irregular intervals until January, 1946, when she was hospitalized elsewhere. The uterus was described as semicystic and enlarged to the size of a 3 months' pregnancy. On Jan. 25, 1946, subtotal hysterectomy was performed. A necrotic semigelatinous mass filled the endometrial cavity. Microscopically, the tumor consisted of atypical glandular epithelium which had invaded the myometrium. The cells and nuclei varied in size and staining characteristics and many mitotic figures were present. The stroma contained cells of irregular size

*This case appears to be identical with one of the two cases of carcinosarcoma of the uterus reported by Lisa, S. R., Hartman, H., Bayer, L., and Bonar, L. D.: *Ann. Surg.* 127: 738, 1918.

22. Corsecaden, Fertig, and Gusberg (1946) reported 9 malignant lesions of the endometrium, including 1 adenosarcoma, among 958 patients who were followed an average of 6.7 years after a radiotherapeutic menopause.

23. Taylor and Becker (1947) reported that 4.97 per cent of a group of 531 patients with carcinoma of the corpus had had an artificially induced menopause.

24. Tyrone (1947), in an analysis of 436 hysterectomies, mentioned 7 cases in which cancer of the endometrium developed several years following radium therapy for benign conditions.

25. Rongy (1947) reported one endometrial cancer which appeared eleven years after x-ray treatment of a woman, aged 32 years, with bleeding of benign origin; and another which was discovered five years after 2 applications of intrauterine radium.

26. Kamperman (1947) added 2 more cases of corpus carcinoma in women who had had an x-ray menopause thirteen and twenty years previously.

Present Study

Records of the gynecologic service of the Roosevelt Hospital from 1915 to June 1, 1947, contain 270 cases of primary malignant tumor of the uterine fundus. We have examined the histories of all these patients in an effort to determine the number who had had pelvic irradiation before the diagnosis of uterine cancer was made. Details of previous treatment and diagnosis in other hospitals were obtained whenever possible. All available curettings obtained prior to the diagnosis of the malignant condition were re-examined, and when the original blocks were still available additional sections were cut and studied. In several instances the original diagnosis of hyperplasia of the endometrium was changed to adenocarcinoma, and in 2 other cases carcinoma was discovered in the resectioned curettings which had been diagnosed originally as benign (Taylor, 1932). After excluding these cases in which unrecognized cancer was present at the time of the original treatment, 21 remained in which a malignant tumor of the corpus was discovered subsequent to pelvic irradiation for presumably benign conditions. This represents an incidence of approximately 8 per cent among our patients with fundal cancers.

The cases are summarized in Table I. The ages of the patients at the time of diagnosis of the malignant tumor ranged from 37 to 74 years, averaging 58 years. This does not differ significantly from the average age of patients with carcinoma of the endometrium as reported in the literature and as we have found among our own patients with this disease (56.6 years). Sixteen of the patients had been treated with radium, 4 with x-ray, and 1 with both. The uterine cavity was the site of radium application in all cases but one. The average radium dose in the 11 cases where this could be ascertained was 1,006 mg. hr., ranging from 350 to 1,500. Diagnosis of the curettings obtained at the time of the original radium treatment was available in 12 cases. Endometrial hyperplasia was present in at least 6 of these. Uterine myomas were the indication for irradiation in 7 cases. The time interval between radiotherapy and recognition of the malignant tumor averaged 8.3 years, varying from eight months to nineteen years.

The tumors have been divided into three main histologic groups. Among the 20 lesions of which the exact histologic type could be determined, 11 were adenocarcinomas, 3 were adenoacanthomas, and 6 contained sarcomatous elements. The last group included 2 myosarcomas, 1 carcinosarcoma, and 3 mixed mesodermal tumors which contained epithelium, connective tissue, and cartilage. The main clinical features of several illustrative cases are presented in the following brief abstracts.

and shape, including occasional giant cells. A diagnosis of carcinosarcoma was made by the 3 pathologists who examined the sections (Figs. 2 and 3). Because of her poor cooperation, the patient received only an incomplete course of deep x-ray therapy to the pelvis post-operatively. Vaginal bleeding soon recurred and she was admitted to the Roosevelt Hospital with this chief complaint on Oct. 6, 1946. A large sloughing tumor filled the upper vagina and lower pelvis, completely replacing the cervix. Biopsy of the tumor on several occasions confirmed the earlier diagnosis of carcinosarcoma.

CASE 15.—P. G. (R. H. No. 21167 and No. 341099), a 52-year-old married Negress with one child, was admitted to the hospital on Dec. 6, 1933, because of a pelvic tumor and pain in the back and legs. Seven years previously she had received elsewhere a cycle of eight x-ray treatments to the pelvis because of this tumor and had been amenorrheic since. Her uterus was irregularly enlarged by a mass about 8 cm. in diameter. On December 28, subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed. The anterior surface of the fundus contained a degenerated myoma, section of which showed large irregular spindle cells with atypical nuclei and mitotic figures (Fig. 4). This tumor was diagnosed as a myosarcoma. The uterus also contained several smaller subserous and intramural benign myomas. Sections of the adnexa were negative. On Feb. 1, 1934, eight 5 mg. needles of radium were inserted into the cervical tissue about the external os, where they were allowed to remain for forty-eight hours, giving a total dose of 1,920 mg. hr. Despite high voltage x-ray therapy, her abdominal pain and backache grew worse and she was readmitted on March 16. A large nodular mass was now palpable in the epigastrium. Roentgenogram of the chest showed several rounded shadows in the lower half of the right lung field which were described as characteristic of sarcomatous metastases. Soon after admission, both legs became paralyzed. The patient grew weaker rapidly and died in uremia on April 20, 1934. At autopsy, sarcomatous metastases were found in the lungs, heart, liver, pancreas, intestines, and abdominal lymph nodes.

CASE 16.—E. S. (R. H. No. 14733 and No. 15759), an English widow of 67 years, was admitted to the hospital on Sept. 17, 1926, because of intermittent vaginal discharge, first watery, then bloody, of a year's duration. She had had a myomectomy elsewhere twenty-two years before, at age 45, at about the time of her menopause. Four years before admission, a submucous hyalinized uterine myoma was removed vaginally at the Memorial Hospital and intrauterine radium was administered, but no details concerning dosage are available. On admission, several polypoid bleeding masses were protruding from a normal appearing cervix. Neither the fundus nor adnexa were palpable. Curettage was performed on Sept. 27, 1926, and 50 mg. of radium were inserted into the uterine cavity for twenty-four hours, giving a total radium dose of 1,200 mg. hr. Microscopically, the curetted tissue presented the typical appearance of a benign endocervical polyp. About a year later, vaginal bleeding recommenced; the patient was readmitted to the hospital on Nov. 1, 1927. The cervix was now dilated by two large purple tumors which were avulsed. Microscopic sections showed a myosarcoma with myxomatous degeneration. The preserved areas of the tumor, which were abundantly supplied with capillaries, contained spindle-shaped cells with large hyperchromatic nuclei and many mitotic figures (Fig. 5).

CASE 18.—F. B. (R. H. No. 18480), the mother of four children, had been treated with 1,200 mg. hr. of intrauterine radium by Dr. James A. Corscaden on Jan. 18, 1918, following a curettage in her home. The curettings were reported as "benign" but no detailed description was recorded. The patient was admitted to the Roosevelt Hospital as a private patient of Dr. Howard C. Taylor on Sept. 17, 1930, at age 61, complaining of backache, lower abdominal discomfort, and cystitis. The uterus reached to the level of the umbilicus. On the following day, total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterine cavity was distended by what appeared to be a submucous myoma, which measured 15 by 12 by 10 cm. Histologically, the tumor was classified as a malignant mixed tumor (adeno-sarcoma) of the uterus. Numerous islands of cartilage were present, surrounded by large vesicular cells and occasional giant cells (Fig. 6). Other areas contained

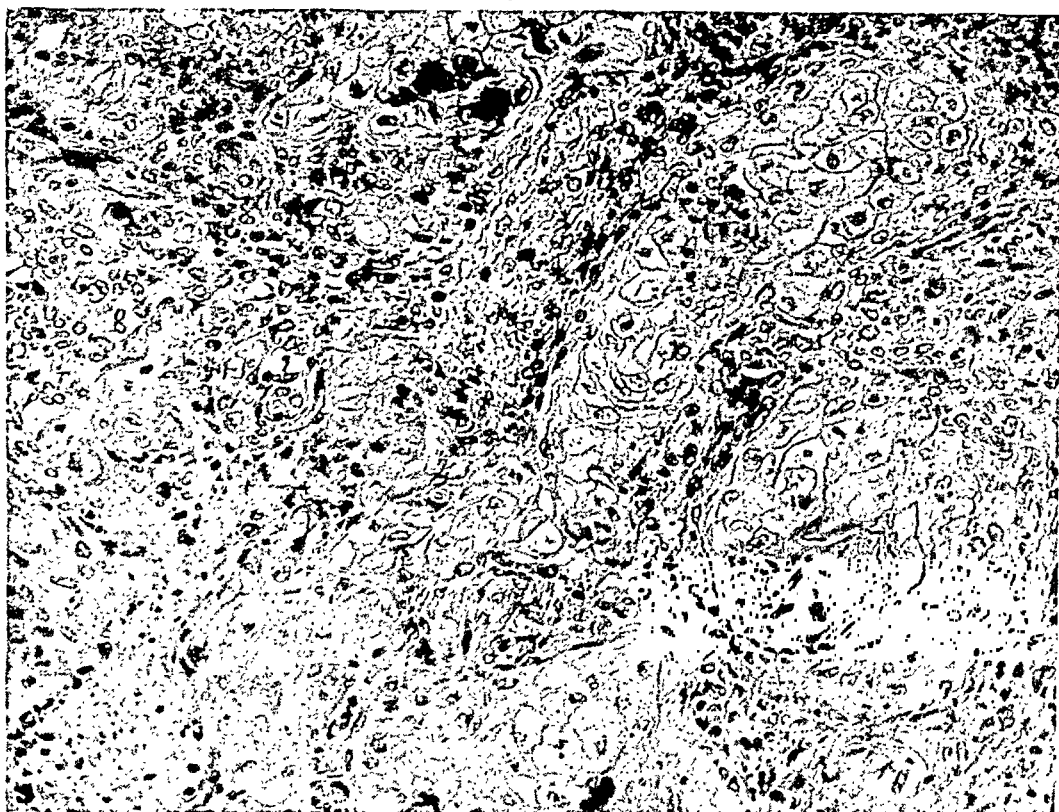


Fig. 1.—Case 14. Adenoacanthoma of endometrium in patient aged 56 years, thirteen years after treatment with intrauterine radium for endometrial hyperplasia.



Fig. 2.—Case 17. Carcinosarcoma of fundus in patient aged 54 years, ten years after treatment with intrauterine radium for myoma. Section shows glandular elements of tumor.

islands of high columnar epithelium with small darkly staining nuclei. This case was included in the study of Corseaden, Fertig, and Gusberg (1946).

Comment

The important clinical question to which an answer is sought is whether pelvic irradiation influences the subsequent development of neoplastic disease of the uterine fundus. Others have studied this problem by observing the incidence of fundal cancer in a series of patients previously treated for benign pelvic conditions. Corseaden, Fertig, and Gusberg found the number of patients who developed the disease in such a series to be 3.4 times as large as the number expected in a random population of the same age distribution. They attributed this disparity, however, not primarily to the irradiation, but rather to the original condition for which the treatment was given; that is, pathological uterine bleeding, often associated with endometrial hyperplasia. In the present series also, hyperplasia was present at the time of original treatment in at least 6 of the 12 cases in which the diagnosis of the curettings was available. This observation offers some support to the claim for an association between hyperplasia and carcinoma of the endometrium (Taylor, 1932; Novak and Yui, 1936).

Another observation, subject to the same difference of interpretation, concerns the relative incidence of previous pelvic radiotherapy among patients who subsequently developed corpus cancer and those with cervical cancer. In the Roosevelt Hospital, carcinoma of the cervix has been slightly more than twice as common as fundal neoplasms. Only two patients with cervical cancer, however, out of a total of 622, gave a history of a previous radiotherapeutic menopause, an incidence of 0.3 per cent. This figure contrasts with the 8 per cent incidence of previous pelvic radiotherapy among 270 women with neoplasms of the corpus. In other words, previous irradiation of the uterus was 27 times as common among patients with corpus cancer as among those with cervical cancer. This finding is in general agreement with the experience of others. Did the radiant energy bear any causal relationship to the later development of the fundal neoplasms?

Those who would answer this question in the negative call attention to the low incidence of uterine cancer among large series of women who have had pelvic irradiation for benign conditions. This approach, although valid in principle, is vitiated by the incompleteness of the follow-ups and by their comparatively short durations. Even in the study of Corseaden, Fertig, and Gusberg, for example, where a high incidence of cancer was found, only 958 of their 1,108 patients were followed, and in 359 (37 per cent) the follow-up period was less than two years. In the present series, the average latent period between radiotherapy and recognition of the fundal tumor was 8.3 years, 19 years elapsing in one case.

Martland, in 1931, reported his detailed study of the cases of osteogenic sarcoma that had occurred among radium dial painters. In the same paper he called attention to the high incidence of primary carcinoma of the lung in miners working with radioactive ores, as in the cobalt mines of Schneeberg and the pitchblende mines of Joachimsthal. It is a well-known clinical fact that irradiation of certain tissues, such as the skin, may cause hyperplasia of the epithelium

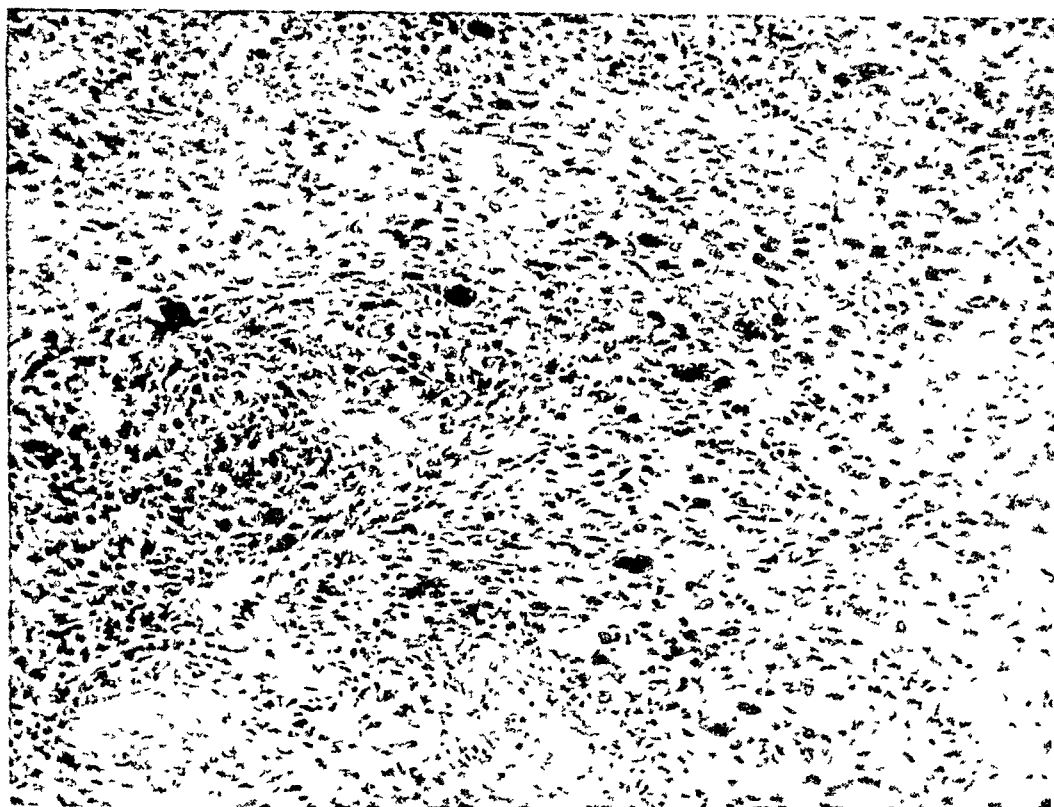


Fig. 3.—Same as Fig. 2, showing sarcomatous pattern. Note giant cells.

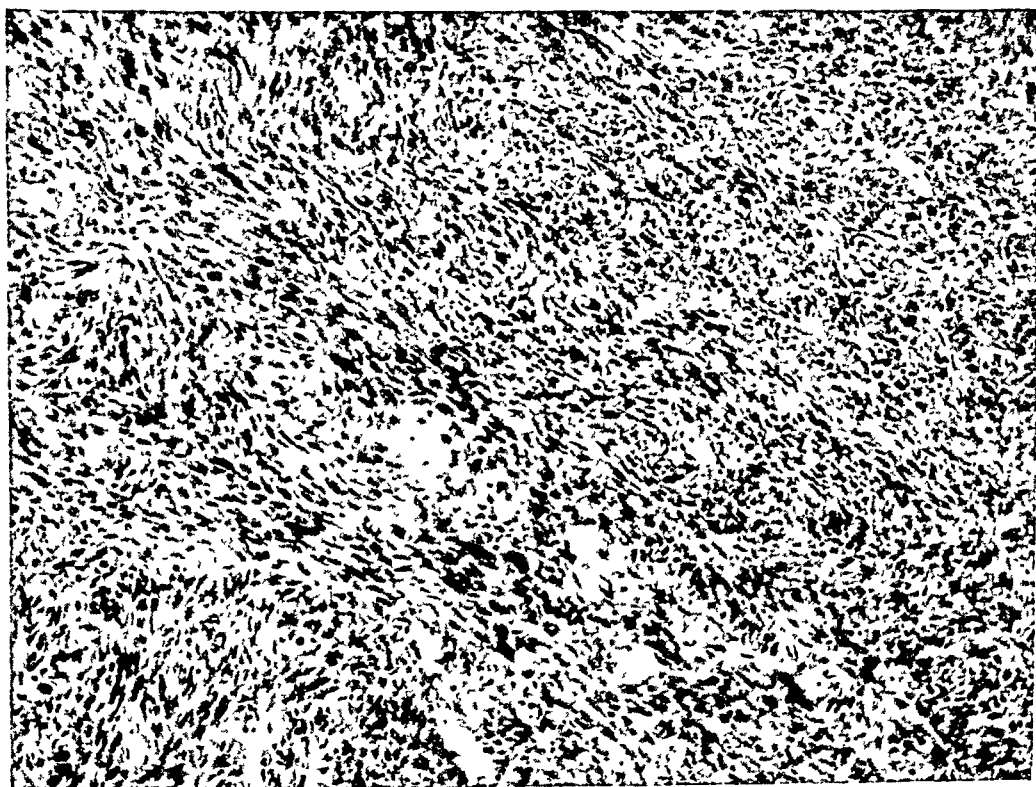


Fig. 4.—Case 15. Myosarcoma of uterus in patient aged 52 years, seven years after x-ray irradiation of myoma.

and in some cases, especially if the irradiation is oft repeated, leads to malignant transformation. Several case reports which clearly incriminate roentgen or gamma rays as carcinogenic agents for skin, bone, and mucous membranes attest the long silent period, frequently 20 years or more, before the development of the clinically recognizable malignant tumor (Burrows, 1928; Kruchen, 1937; Florentin, Jacob, and Hun, 1946; Glover, 1947; Cahan et al., 1948).

Exposure of the human ovary to sterilizing doses of x-rays results in atresia of the follicles. If the dose is small, a certain proportion of the primordial follicles may escape (Desjardins, 1932). Even after fairly intensive irradiation, the ovaries may retain their capacity for estrogen production although the ova have been destroyed (Miller, 1930). Kaplan (1939, 1945) reported the case of a young girl who had normal menses despite pelvic irradiation with 3,300 r. of x-ray and 990 mg. hr. of radium. Experimentally, Schmidt (1938) has found that irradiation of the ovaries of guinea pigs with a minimum sterilization dose of x-rays leads to the replacement of the normal ovarian structure by "interstitial gland" and cysts, accompanied by prolonged estrus with mammary gland development and urinary excretion of estrogen. Within a year, endometrial cysts were common; and in two years the uterine glands were irregular, distorted, and increased in number. The postmenopausal years in the human being are associated with an increased production of follicle-stimulating hormone. Essenberg (1947) has recently shown that the x-ray damaged ovaries of young mice respond to this substance with the production of active germinal epithelium and the formation of young follicles, although their ova soon atrophied. Even in the absence of extraneous hormonal stimulation, the mouse ovary, after recovery from its initial depression from exposure to x-rays, undergoes a phase of regeneration in which proliferation of the germinal epithelium and granulosa cells occurs to such a degree that granulosa-cell tumors often result (Furth and Butterworth, 1936; Traut and Butterworth, 1937; Geist, Gaines, and Pollack, 1939). The endocrine function of these tumors was indicated by the endometrial hyperplasia and the increased incidence of mammary tumors in the mice which bore them. Traut and Marchetti (1940) mentioned 2 cases in which granulosa-cell tumors were found in women who had had previous treatment with intra-uterine radium, but they carefully avoided attaching any significance to this observation.

Even less than x-rays would a menopause-inducing dose of intrauterine radium be expected to cause a cessation of ovarian function. The cancericidal emanations from radium placed within the cavity of the uterus extend over little more than a radius of 3 cm. Effects of smaller doses on ovarian hormonal production are variable. Neumann and Péter (1932) demonstrated estrogenic hormone in the blood of several patients many months after the induction of a radium menopause with 2,500 mg. hr. of the element. It is possible that in some cases the amenorrhea which results from intrauterine radium depends primarily on its local sclerosing effect on the uterus.

There is considerable evidence to the effect that the estrogenic factor is important in the genesis of endometrial cancer (Taylor, 1944). In another

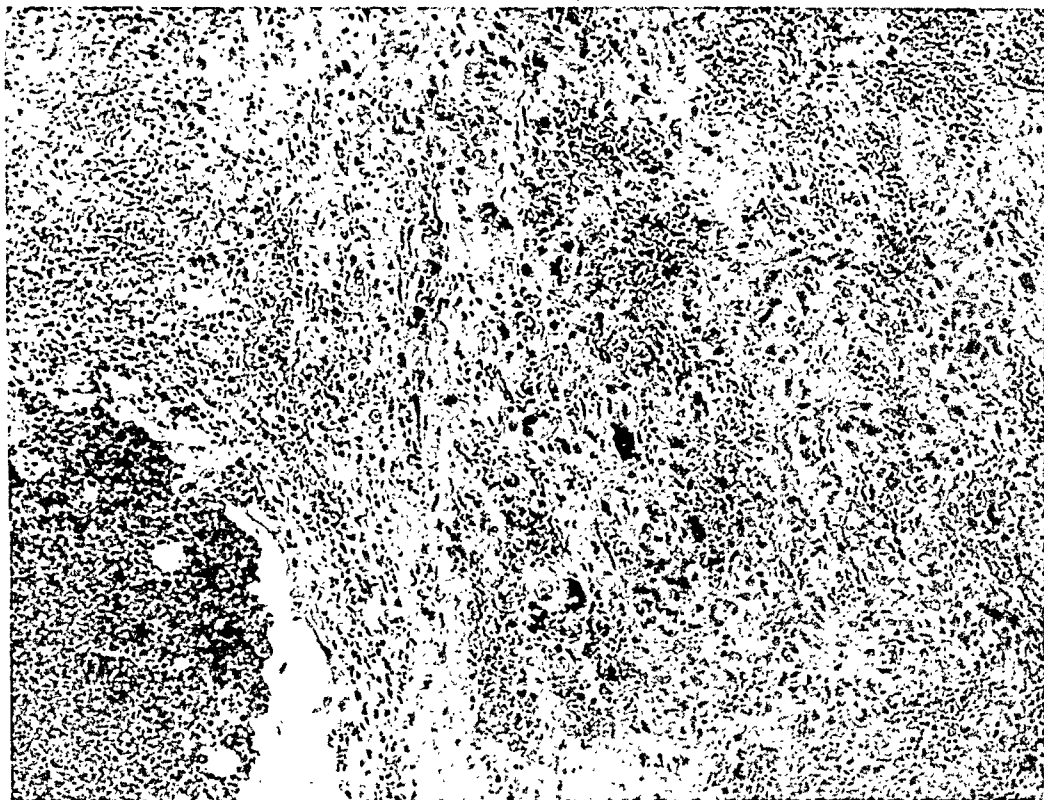


Fig. 5.—Case 16. Myosarcoma of uterus in patient aged 67 years, five years after treatment with intrauterine radium for a myoma and one year after treatment with intrauterine radium for an endocervical polyp.

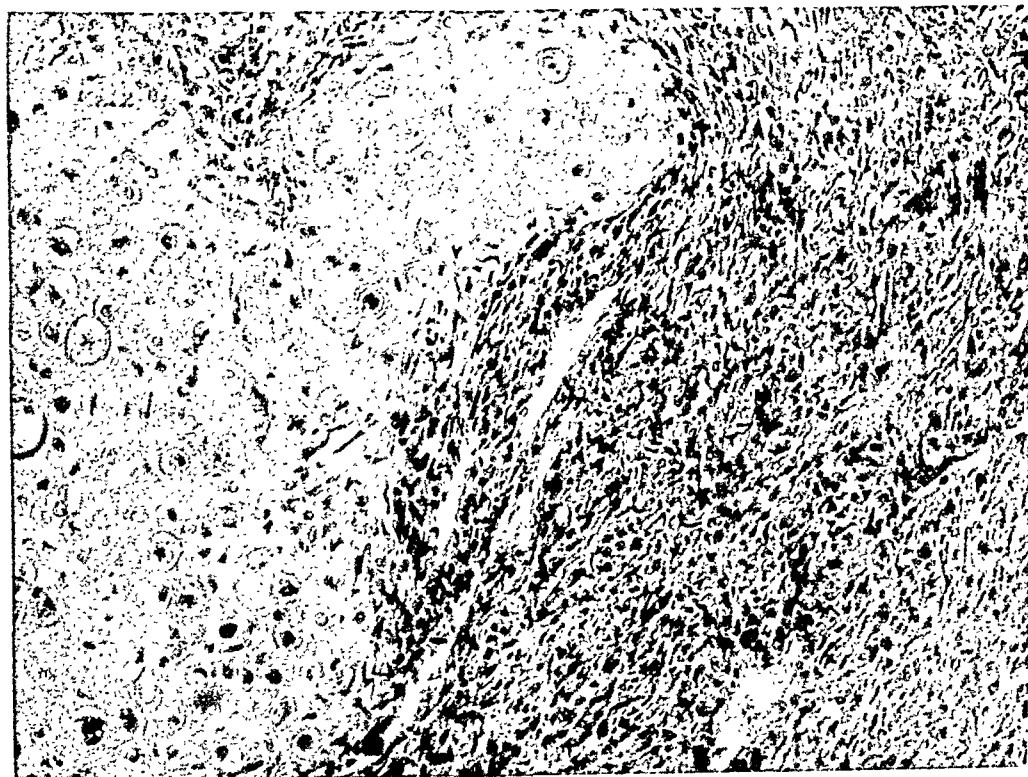


Fig. 6.—Case 18. Mesodermal mixed tumor (adenosarcoma) of the uterus in patient aged 61 years, twelve and one-half years after treatment with intrauterine radium. Note cartilage in tumor.

appearance of the tumors was $1\frac{1}{2}$ years. Neither inflammation nor irradiation alone sufficed to produce the tumors; both were required. These experiments were repeated and the results confirmed by Burrows, Mayneord, and Roberts (1937) and by Burrows and Clarkson (1943). The latter authors stated that the possible danger of causing neoplasms in man by irradiating inflamed tissue has been overlooked because of the long interval between cause and effect. The human endometrium almost always shows evidence of a chronic inflammatory reaction after a period of prolonged bleeding. Irradiation of such uteri perhaps fulfills the requirements for the induction of sarcoma as established experimentally. Recent experiments by Figge (1947a, 1947b) have further interest for the problem. This author found that the intensified cosmic rays to which mice were exposed when their cages were covered with lead plates resulted in a decreased latent period for the appearance of subcutaneous sarcomas following the injection of methyleholanthrene. Radium has caused osteogenic sarcomas to develop in rats (Dunlap et al., 1948).

More recently carcinoma of the uterus has been produced in rabbits by exposing the animals to x-rays (Lorenz, Eschenbrenner, Heston, and Deringer, 1947).

The evidence presented in this paper falls short of proving that radiant energy is carcinogenic for the human uterus. Combined with the clinical and experimental data in the literature it is believed to be sufficiently suggestive, however, to warrant further study of the problem and to temper, in the meantime, the enthusiasm which many gynecologists have for pelvic irradiation in the treatment of benign conditions of the uterus. Figge (1947c) has formulated a concept of cocarcinogens, suggesting that cancer may be caused not by a single substance but by two, three, or more interdependent noncarcinogenic agents. It is possible that radiant energy may fall into this category. The following excerpt from a recent editorial in the *Journal of the American Medical Association* (Vol. 138, 214-215, Sept. 18, 1948) seems pertinent: "Roentgen treatment for benign conditions should be used only with a vivid appreciation of its capacity for harm and with an overt evaluation of its presumptive benefits weighed against the known and possible injuries inseparable from its use in effective dosage."

Summary

1. Twenty-one patients among 270 with malignant tumors of the body of the uterus (8 per cent) gave a history of previous irradiation of the pelvic organs with radium or x-rays for benign conditions. The incidence of previous pelvic irradiation among patients with cervical carcinoma, by contrast, was only 0.3 per cent.

2. Six of the 21 tumors contained sarcomatous elements. This was five times the incidence of sarcomas among all the malignant tumors of the uterine fundus.

3. The average time interval between irradiation and detection of the uterine cancers was 8.3 years.

4. These findings, together with previously published data in the literature, suggest a possible carcinogenic effect of radiant energy on the human uterine fundus.

paper, additional evidence will be presented to support this view. Carcinoma of the endometrium is exceedingly rare following surgical castration. Radiotherapeutic "castration" lacks this prophylactic effect. The difference is probably ascribable in part to the continued production of estrogen by the ovaries of at least some patients who have been subjected to a radiation menopause.

Many gynecologists have the impression that the incidence of endometrial cancer is on the rise. This impression is substantiated by the records of the Roosevelt Hospital. The average annual number of cases of this disease treated in this clinic during 1945 and 1946 was approximately double that for the preceding eight years, although the clinic population has remained practically stationary. Several possible factors may be mentioned in explanation of this increase; namely, an increasing life span of the population, more frequent resort to curettage, and improved diagnosis. Two additional factors of possible significance are the common use of estrogens for menopausal symptoms during the past decade, and the treatment of benign pelvic conditions by irradiation, a method of treatment which has been in popular use in this country during the past 25 years. In 5 of the 21 cases in the present series the diagnosis of fundal cancer was made during the last two years.

A disproportionate number of sarcomas appear in the literature among the reported cases of malignant tumors of the uterine corpus which occurred following pelvic irradiation. Vogt (1926) reported 3 sarcomas to 3 carcinomas; Martindale (1933) recorded a sarcoma of the fundus and one of the cervix to 2 endometrial carcinomas; Scheffey (1942) had 1 sarcoma to 4 carcinomas; and Burnam (1942) observed 1 sarcoma to 5 carcinomas. In a study of 20 cases of sarcoma of the endometrium, McDonald, Broders, and Counseller (1940) noted that 2 of their patients had had the menopause induced previously by means of radium or x-rays. Novak and Anderson (1937) reported a case of polypoid cervical sarcoma in a 38-year-old woman in whom an x-ray menopause had been induced 8 years previously because of uterine bleeding.

The histologic classification of the 21 cases in this series likewise shows an unexpectedly high incidence of 6 sarcomas (29 per cent), whereas the incidence of sarcomas among all the malignant tumors of the fundus recorded in the clinic is only 6 per cent. Carcinosarcomas and malignant mixed tumors have been classified as sarcomas. Of the 4 patients with malignant mixed tumors of the fundus who have been treated in the Roosevelt Hospital, 3 had a history of treatment with intrauterine radium for benign conditions nine to fourteen years previously. The reader is referred to the paper by Liebow and Tennant (1941) for a description of this type of tumor and a review of its literature. Another finding of incidental interest was the 3 cases of adenoacanthoma, an uncommon but by no means rare type of endometrial neoplasm.

The significance of the high incidence of sarcomatous tumors among previously irradiated uteri is brought into clearer focus by a consideration of experiments begun in 1933 by Lacassagne in France. This worker found that sarcomas could be produced in the thighs of rabbits by a single exposure to 610 r. of high voltage x-ray following the induction of a local inflammatory lesion with either bacteria or sterile irritants. The average latent period for the

A TECHNIQUE TO AID IN THE DETECTION OF MALIGNANCY OF THE FEMALE GENITAL TRACT*

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NOTWITHSTANDING the expenditure of large amounts of energy and money, the cancer problem has not been solved. Unquestionably, a great deal has been learned about atypical growth, but significant clues to the origin of malignancy are few. Most of the studies seem to fall fairly readily into three groups. One of these has been the search for a causative agent, a virus, or some other initiating factor. No less important has been the work of the chemists studying the metabolism of malignant cells, the enzyme systems involved, and the effects of various circulating chemicals in the blood, such as hormones. Finally, there has been a number of studies pointing to the importance of the constitutional or genetic factor.

There is, however, another aspect to the problem to which little attention has been given. Malignant cells not only seem to be different chemically from normal cells but, more particularly, they exhibit profound disturbances not so much in the character of individual cells as in the relationship which cells bear to each other. In normal growth and differentiation, changes occur not only in the internal pattern of each individual cell, but also in the way these cells are grouped and linked together to form characteristic tissues and organs. In malignancy, it is this necessary relationship between cells that is lost. The basic problem, therefore, is: What has happened to the forces which in normal growth define the pattern of organization of tissue and organs of the whole organism? This, of course, is another way of saying that cancer is but a special case of the central problem of all biology, the origin of design of the living system; for it is the breakdown of the forces of organization which is at the heart of the problem.

Explanations of the origin of design have been offered by Aristotle, Descartes, Driesch, and Childes, to name but a few, but they have not been entirely satisfactory. As natural-history descriptions of biologic events, these have been interesting, unquestionably, but as sharply defined descriptions of the nature of the forces involved, they have been of little help.

A number of years ago, consideration of the problem of organization of the developing nervous system led to an attempt to solve this problem in a different manner.^{1, 5, 13} Since it has long been known that electrical activity is a common

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variations in biologic activity are correlated with variations in the electrical characteristics of the field. It is these variations in field properties that can be measured in part by means of determination of standing potential differences. However, such measurements, in order to be consistent and reproducible, ideally must be made as pure voltage gradients independent of current and resistance changes. For this purpose, the electrometer of the physicists should be the instrument of choice. Unfortunately, this is a difficult instrument to handle except under very rigorous conditions. To simplify the problem, therefore, a vacuum tube microvoltmeter was designed⁶ with sufficiently high input impedance to reduce current and resistance in the system being measured, to a negligible value. The circuit developed is essentially a Wheatstone bridge, using two vacuum tubes or a twin tube, and fixed resistance as the third arm in the bridge, with the potential differences to be measured imposed across 10 megohms on the fourth arm of the bridge. Any voltage gradient across the 10 megohms unbalances the bridge so that the resulting changes in plate current can be read on a suitable galvanometer. Again, the potential difference must be read by means of some contact with the living system which does not develop self-potentials and which are completely reversible. For this purpose, silver-silver chloride electrodes were chosen, operating in physiologic salt solution, which latter is brought into contact with the living organism through any convenient procedure. Finally, since this technique reports changes in potential differences in the inherent field, it is possible to make a great many determinations without disturbing the system measured.

The particular instrument used in this study consists of a twin triode, 2-C21, 1642, in a bridge circuit employing a cathode follower (Richter). The cathode follower resistance is variable and by means of the double pole, double throw input switch the control grid can be balanced at free grid potential. This is an absolutely necessary condition of operation. Power is supplied to the bridge through a standard power pack which, however, must be operated in conjunction with a voltage regulating transformer (Solar). The output from the plates is fed to a General Electric photo-electric recorder with a 3 micro-ampere full scale deflection. The galvanometer in this instrument should have critical damping resistance of approximately 10,000 ohms. By interposing a 10,000 ohm potentiometer between the output of the bridge and the input to the galvanometer, the over-all sensitivity can be set at any desired multiple of one millivolt per unit deflections. Since virtually no current is drawn from the system measured, null point determinations are unnecessary and the recorder can be used as a straight deflection instrument. A complete circuit is shown in Fig. 1.

Calibration of the apparatus can be most easily performed using a Leeds and Northrop student type potentiometer. With this, it is possible to introduce into the microvoltmeter any desired number of millivolts. These will be recorded by the movements of the pen in the recorder. The connection of the electrodes to the instrument and of the instrument to the recorder should be so arranged that when the pen moves to the right of the zero point, the "hot" or control electrode will be positive to the reference electrode by the imposed number of millivolts. Conversely, movement of the pen to left of the zero point means that the control electrode is negative to the reference electrode by the imposed number of millivolts. Normally, it has not been found necessary to ground any part of the apparatus, but there are circumstances when a ground is necessary, especially where there is a good deal of other electrical apparatus in the environment. This is accomplished by running a lead from the reference electrode binding post to any suitable external ground. It may be advisable to shield the leads from the electrodes to the instrument. Finally, the table on which the

attribute of living systems, it was suggested that such electrical manifestations were evidence of an electrodynamic field in all living beings, and that it was this field which, through its inherent forces, imposed design on living matter. Evidence supporting this hypothesis has been accumulated and has been summarized recently.^{4, 13, 14}

If, then, cancer is a special case of the problem of organization, it should follow that atypical growth should be accompanied by significant alterations in the characteristic field properties of a living organism. That this is the case has been shown in studies of malignancy in mice.^{3, 7, 8, 9} In all these studies, however, it was very disappointing to find that, while the changes in the field were statistically significant, they were useless so far as the individual organism was concerned. A number of factors probably explain this lack of individual significance. Biologic variation of both the host and the growth, the unfortunate necessity of tying the animal down for observations, and the relatively low potentials obscured the final results. However, the statistical evidence was sufficiently strong to warrant the extension of the procedure to the problem of cancer in human beings.

In the clinic, there are numerous diagnostic techniques with which electrometric records can be correlated. A careful study may, therefore, yield significant results in at least three cases. In the first of these there may be uncovered a significant electrometric correlate of malignancy. Secondly, there may appear a significant relationship between the electrometric findings and the rate of development of malignancy. Finally, since all these results derive from the field properties which define the design of the organism, it may be that an electrometric pattern will be found which can either indicate the existence of malignancy before the other standard methods of analysis or perhaps predict the constitutional type which may, at some later period, and under proper conditions, develop cancer.

Finally, if these studies should yield significant results, it would follow that cancer is a defect in the design of the organism which a wide variety of causative agents may be expected to uncover. There would be, therefore, no cause of cancer in the sense of an agent, but rather a constitutional or field defect which may develop into cancer as a result of any one of a wide number of external or internal factors.

To test the above hypothesis, an experiment was set up on the Gynecological Service of Bellevue Hospital. The technique employed follows in detail, in the hope that similar studies in other clinics will be carried out. The results of the first 428 cases are included as a preliminary report. The study is, at present, being continued with a grant from the National Cancer Institute of the United States Public Health Service and the clinical results will be published at some later date.

Technique

A number of primary assumptions underlie the application of direct current measurements to a cancer problem. The first of these is that the living system possesses as one of its attributes an electrodynamic field. A second is that

patient lies should be insulated on glass cups and all parts of the instrument should be supported on insulating material. In rooms to which run alternating current lines, adequate grounding of the apparatus may be necessary.

The electrodes used are standard silver-silver chloride electrodes made by chloriding pure silver wire in molar hydrochloric acid at 40 milliamperes for five or ten minutes.* (Fig. 2.) The reference electrode which was placed on the ventral abdomen just above the symphysis pubis, is shown at *A* in Fig. 3. The holder can be readily constructed from a short segment of lucite rod. The center of this is drilled out to make a deep cup and a hole drilled through the side wall into which is cemented a short length of smaller diameter lucite tubing. A castolite casting may also be used. (Fig. 3.) The silver electrode may be inserted into this side arm with the active end of the electrode in the bottom of the well. The well can then be packed in cotton soaked in physiologic salt solution. This type of holder has certain advantages in that it can be made rapidly and the cotton plug can be replaced after each measurement. An air filter, such as is used to aerate aquaria and which, therefore, is porous, may be drilled out to make a chamber in which the exposed tip of the silver-silver chloride can be placed. A side arm of amphenol tubing to hold the electrode in position is cemented on. All but the flat face of the chamber is then given several coats of a waterproof plastic—in this instance, Phenoplast. This unit, when soaked in physiologic salt solution, provides adequate electrical contact with the skin. The vaginal electrode was constructed from a piece of lucite tubing, approximately one-half inch in diameter, formed into a shallow *S* curve after heating in boiling water, and the whole interior filled with paraffin after insertion of the silver wire. The active portion of the electrode projects a quarter of an inch beyond the lucite tube and may be covered, after chloriding, with cotton or gauze soaked in saline or, as in the final form, by a small section of filter tubing. This electrode is diagrammed at *B* in Fig. 3. Electrodes made in the above manner do not develop significant self-potentials over a considerable period of time. Usually it is wise to have a second pair available. If, however, a small potential difference, not to exceed 2 to 5 millivolts, appears between the electrodes when immersed in common salt solution, they can still be used. It is simply necessary, after immersing the two electrodes in common salt solution, to bring the recording pen to the arbitrarily selected zero in the center of the recording paper by means of the zero controls. (Fig. 1.) The reference electrode is then placed on the abdominal skin, with the patient in a recumbent position, and held there by any convenient bandage. The vaginal electrode may then be introduced, placing the protected tip in the posterior fornix of the vagina against the cervix. With the patient resting quietly and undisturbed by the electrode placement, a continuous record of the potential difference between the ventral abdominal wall and the cervix can be recorded for any convenient length of time, usually from fifteen minutes to one-half hour. At the start of such a record, there is often a drift to either negative or positive side of the zero point. This is not always present, but probably indicates that the whole electrode system is coming to equilibrium with the living organism. For the rest of the run, the potential difference will usually remain astonishingly constant with only minor variations. At the conclusion of the run, the two electrodes should be removed and placed in a common bath of salt solution. Any change in the zero point should be noted. This, however, rarely occurs if the technique is correct.

Finally, a word of caution. This is a highly specialized technique. The instruments are exceedingly sensitive and must be handled with care and with

*More recently, Dr. Theodore Shedlovsky prepared for this study a pair of electrodes made by fusing chemically pure silver chloride directly to the silver wire. These have proved eminently satisfactory.

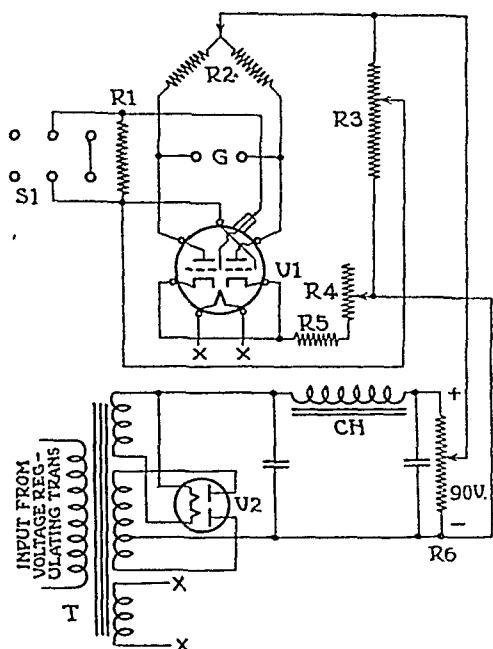


Fig. 1.

Fig. 1.—Microvoltmeter circuit. S1—General radio switch, type 339-B, R1—10 megohm resistor, S. S. White, R2—10 K helipot, R3—100 K 50W. Semivariable. Clarostat tap at 65 K ohms, R4—10 K General radion potentiometer type 301-A, R5—20 K fixed wire wound IRC, R6—Same as R3, T—Transformer UTC R-2, CH—Choke, G—Galvanometer in G.E. photoelectric recorder, V1—RCA Twin Triode 2C21/1642, V2—RCA rectifier type 80 or equivalent.

Fig. 2.—Circuit for chloriding electrodes.

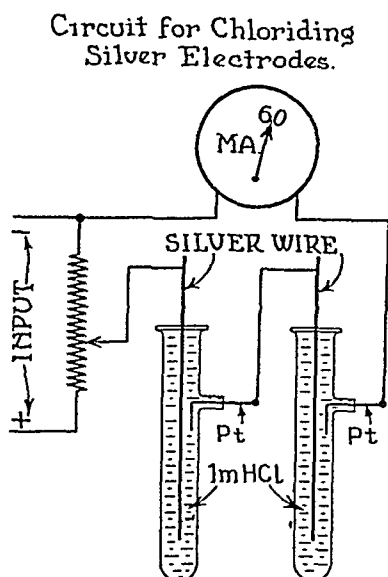


Fig. 2.

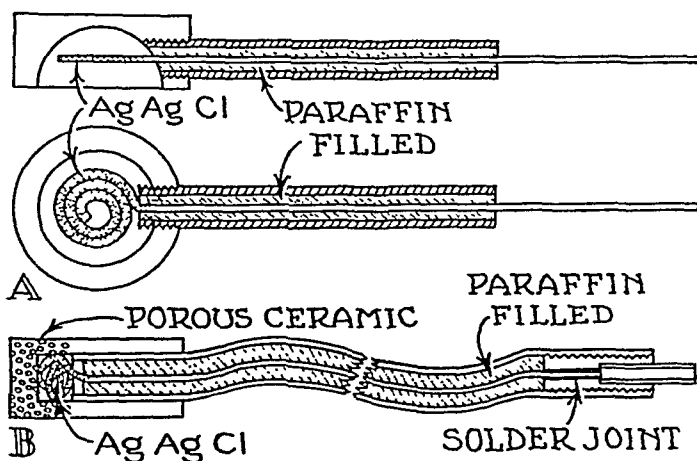


Fig. 3.—Diagram of plastic holders for electrodes. Connections of silver wire to leads to micro-voltmeter must be protected from moisture.

Finally, however, the fundamental assumption on which this study is based suggests that the negativity in many of these patients may have predictive value. It is not at all impossible that these patients, although they have not yet shown clinical signs of malignancy, may possess the field defect which will, at some later date, and under the proper conditions, result in cancer. This possibility is so important that an adequate follow-up study should be made on these patients. They should be examined electrometrically at fairly frequent intervals for as long a period as possible, but not for less than five years.

This brief summary of the results on four hundred twenty-eight cases confirms the basic hypothesis that cancer is fundamentally the result of a failure of the organizational field forces in the living system. When measures of these field forces are properly made, obvious differences in the field properties of patients, with or without malignancy, have been determined. In three hundred fifty-three nonmalignant cases, two hundred eighty-nine showed the cervix to be positive with respect to the abdomen. A polar reversal of the field forces between the cervix and the ventral abdominal wall has been found in malignancy. This polar reversal is also found in 18.1 per cent of the nonmalignant pathology and in normal individuals.^{10, 11}

It is to be noted that this study results from a deductively formulated theory of biologic organization derived from the postulational concepts of modern field physics. This theory was required by the inadequacy of chemical and thermodynamic concepts to explain the persistence of the necessary relatedness between the constantly changing entities of biologic systems.¹⁵ In cancer, the primary defect is a breakdown in the normal controls of this necessary relatedness. Field forces are adequate in magnitude and direction for these controls. Hence, measurable alterations in the fields, showing departure from the paradigm, correlate with malignancy, which is the result of the breakdown of controls of the pattern of organization in the living system.

Summary

1. A technique is described for measuring field forces in the intact human being.
2. In seventy-five patients with cancer of the female genital tract, seventy-four showed the cervix to be consistently electronegative to the ventral abdominal wall, 98.7 per cent.
3. Three hundred fifty-three patients with nonmalignant pathology showed the cervix to be electropositive to the ventral abdominal wall in two hundred eighty-nine instances, or 81.9 per cent.
4. In two hundred ninety patients showing the cervix to be electropositive to the ventral abdominal wall, two hundred eighty-nine, or 99.6 per cent were in nonmalignant conditions.
5. Sixty-four patients, or 18.1 per cent of those with nonmalignant conditions, showed an electronegativity of the cervix similar to that found in cancer.
6. It is suggested that an unknown number of this latter small group may represent patients with field defects who may, at some later date, develop cancer.

understanding. There are many pitfalls which can be avoided only by practice and patience. The procedure, however, once mastered, becomes relatively simple, although never foolproof. Reproducible results come only after experience.

Discussion

The results of the study utilizing the technique described above are still far from complete, but a brief summary of four hundred and twenty-eight cases is presented as a validation of the procedure.

These cases fall into two clinical groups. Seventy-five patients belong in the group diagnosed clinically, and by pathological examination, as having malignancy in various stages of development; involving the cervix in sixty-one cases, the fundus in seven, the ovaries in six, and one patient in whom the malignancy was thought to be primary in the bladder.

Three hundred fifty-three patients fall into two groups, one with a wide variety of nonmalignant pathology, and one with no demonstrable pathology. Electrometrically, all but one of the first group showed a very evident electro-negativity of the cervix with respect to the ventral abdominal wall. Only one case diagnosed as malignant gave a positive record. The magnitude of the negativity varied from patient to patient. There was no clear-cut correlation between this magnitude and the stage of malignancy. In at least one instance, although the electrometric record was negative, the pathologic report was equivocal. On a second biopsy, however, material was obtained from which a positive diagnosis of malignancy was obtained.

In the group of nonmalignant pathology, three hundred fifty-three in number, two hundred eighty-nine, in contrast to the first group, showed a significant and marked positivity of the cervix with respect to the ventral abdominal wall. As in the first group, the magnitude of the positivity varied from patient to patient and failed to show any significant relationship to the kind of pathology. The remainder of this second group, sixty-four, showed an electrometric negativity identical with that found in the cancer group.

The reasons for this finding are not entirely clear. There are, however, a number of possibilities. In the first place, eleven of these negative cases were fibroids. They are generally believed to be nonmalignant growths, but they are also atypical arrangements of uterine cells, hence the field changes may not be unlike those found in malignancy. Six of the patients in this group were intra-uterine pregnancies. These are included to indicate that there are other factors than cancer which may be accompanied by field changes. A third group of eight cases are included because they represent another source of negativity of the genital tract, namely, ovulation. All of these patients were within the ovulatory time and exhibited no obvious pathology. The correlation of negativity with ovulation has been referred to previously.¹¹ Seven patients were post-menopausal and, as will be shown in a later report, a much greater incidence of negativity and malignancy is observed in the older age groups. The remainder of the patients in this group showing negativity of the cervix covered a wide range of pathology, including five ovarian cysts, four abortions, six cases of pelvic inflammatory disease, four cervical polyps, two granulomas of the cervix, etc.

PREGNANCY AND HODGKIN'S DISEASE

With a Report of Three Cases

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THE basis for a rational approach to the management of pregnancy complicated by Hodgkin's lymphogranulomatosis is conceived with great difficulty. Careful search of the literature has revealed only 29 cases of Hodgkin's disease occurring during pregnancy (Table I) which are reported in detail and corroborated by adequate histologic study. The English and American literature has but five reports dealing with this problem, all but Adair⁸ presenting single cases. Only Gemmell² does more than present a case history.

Three patients with Hodgkin's disease complicating pregnancy have been seen in the Tumor Clinic of the Boston Dispensary in the past ten years, of a total of twelve women with Hodgkin's disease admitted during this period. Each diagnosis was confirmed by histologic study, and this report presents the case histories of each patient. An analysis of the earlier reports together with these three cases is considered to be of some value in developing a basis for the management of the obstetric factors in this complex situation. The scarcity of this complication in obstetrics is attested to by the report of Palacios Costa, Chavanne, and Zebel Fernández¹⁴ who found five cases of Hodgkin's disease in 30,000 gestations, or an incidence of 1 in 6,000 pregnancies.

Case Reports

CASE 1.—B.D. No. 394442, Mrs. B. F., para 0, gravida i, abortions 1 (1-0-0-1-0), aged 29 years, was admitted to the Tumor Clinic of the Boston Dispensary on Sept. 22, 1939, with engorgement of neck veins and a roentgenographic picture of mediastinal masses suggestive of Hodgkin's disease. She reported a spontaneous abortion two months preceding her first appearance in the Tumor Clinic. She received 1600 r of external radiation with the 200 k.v. machine to the anterior and posterior chest over the next three months, and her symptoms and signs subsided. A bean-sized node in the left clavicular area was excised and microscopic examination revealed: fibrosis obliterating normal lymph node architecture, marked infiltration with eosinophiles, hyperplasia of the reticulo-endothelial cells, occasional characteristic Reed-Sternberg cells, edema, cellular infiltration of the capsule extending out into the periglandular tissue, and areas of necrosis. A diagnosis of Hodgkin's disease was made. She received an additional 2700 r to the anterior and posterior chest and left supraclavicular areas over the succeeding three months. Her general condition was improved. On April 11, 1940, a diagnosis of intrauterine gestation of fifteen weeks' duration was made, her expected date of confinement being October 25, 1940. The mediastinal shadow continued to enlarge in spite of the roentgen therapy. Obstetric consultation at that time expressed reluctance to advise interruption of the gestation. In the next three months a total of 4500 r were administered to the chest. There developed increasing dyspnea, choking spells, and edema of the neck and clavicular skin area in the last trimester, and 5000 r of therapy was administered to the

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macerated baby with a true knot in the cord. The patient sustained some cervical and vaginal lacerations during parturition for which she was treated with transfusion and streptomycin. She was discharged in good condition but re-entered April 23, 1947, one month post partum, for vaginal bleeding. A dilatation and curettage were performed and placental site bleeding remedied. Examination at that time revealed a small right cervical node and her liver was palpated 1 cm. below the costal margin in the midclavicular line on deep inspiration. She was asymptomatic in remission at the time of this report.

Discussion and Analysis

The clinical and pathologic changes of Hodgkin's lymphogranulomatosis are too well known and widely studied to require comment here. Our concern is entirely with the obstetric aspects of the problem.

Reference to the standard contemporary source books for opinion concerning the management of pregnancy complicated by Hodgkin's disease is of little avail. Stander,¹⁶ De Lee and Greenhill,¹⁷ Davis,¹⁸ Titus,¹⁹ Adair and Stieglitz,²⁰ and Halban and Seitz²¹ do not mention this problem at all. Adair⁸ states that "the effect of Hodgkin's disease combined with pregnancy is not known, but, judging from the two cases who have been registered at the Chicago Lying-in Hospital, the prognosis seems to be unfavorable. Neither of these patients became markedly worse during pregnancy. . . . The possible accelerating effect of pregnancy on the condition and the generally fatal outcome, then, are the reasons for considering pregnancy undesirable in Hodgkin's disease patients." At the present time not a single modern expression of opinion based on more than two cases has been found which would be of value to English readers. Berkeley and Bonney²² in 1913 stated that "Hodgkin's disease may first declare itself during pregnancy, or pregnancy supervening upon it, the course of the disease may be much accelerated." They felt that abortion is very common and that the anemia concomitant with the process may lead to retroplacental and postpartum hemorrhage. In their opinion pregnancy should be terminated. Since there has been no recent analysis of pregnancy complicated by Hodgkin's disease, it was felt that studies of all the cases available might clarify some of the many ramifications of the problem.

Gemmell² studied 57 cases of Hodgkin's disease in women and found that about one-half occurred during the childbearing period. Approximately 16 of these were married, and six of these married women dated the onset of their disease from some pregnancy. In addition, in the 17 women in whom a menstrual history was available, 14 had some degree of oligomenorrhea. Thus, in nearly one-half of the women in his series, the onset of Hodgkin's disease occurred during a period of physiologic amenorrhea. The labors in the six cases available for his study were normal in five instances and presented a postpartum hemorrhage in one case. The puerperium was normal in five cases and febrile in one which expired on the one hundred ninetieth day post partum. Three spontaneous abortions occurred which were not considered related to the Hodgkin's disease. One premature labor (seven months) occurred and was also felt to be incidental. He felt that estrogens played an ameliorating role in the process.

Study of Table I reveals that there are twenty-four parturients in the literature whose age can be established during pregnancy complicated by Hodgkin's disease. The average age of these women is 28.3 years, with 15 falling in the 20- to 29-year-old group, and nine in the 30- to 39-year-old group. The youngest patient reported was 20 years old, and the oldest 39 years of age. Herz⁴ states that the disease is most frequent during the 30- to 50-year-old age period. Epstein²³ reported Hodgkin's disease one-third as frequently in women as in men, and felt the process to be less malignant in women. In 204 cases he found

mediastinal area during this time. Extensive infiltration of both lungs was found in her eighth month of gestation. Almost constant therapy kept this patient moderately comfortable, although a chronic cough and increasing dyspnea persisted. In all, a total of 11,000 r of roentgen therapy had been administered in a period of eight months. Additional tumor masses developed in the mandibular and clavicular areas. Her condition showed progressive deterioration, and she was admitted to the hospital on Aug. 9, 1940, for acute gastroenteritis and again at thirty-four to thirty-six weeks' gestation because of rapid deterioration of her physical state. Labor was started by artificial rupture of membranes, and she delivered by low forceps under local anaesthesia a 2150 Gm. male infant in good condition, who survived for four days. The first few days post partum the course was uneventful and afebrile, but on the eighth day of the puerperium the patient began to go downhill rapidly and expired that evening. Postmortem examination of the baby showed massive atelectasis, and no evidence of damage from the roentgen therapy which had been administered during her pregnancy. The placenta was examined and found to be entirely normal. A postmortem on the mother was not obtained.

CASE 2.—B.D. No. 4137, Mrs. E. G., aged 20 years, was first seen in the Tumor Clinic of the Boston Dispensary on Dec. 23, 1941, for a bulge in the left supraclavicular fossa. Biopsy of these glands revealed the typical findings of Hodgkin's lymphogranuloma in the stage of almost complete sclerosis. She received 200 k.v. machine roentgen therapy to this area (600 r) and later to the skull for severe headaches which were considered to be on the basis of the Hodgkin's disease. She remained in a state of remission for three years when she again received 450 r at 200 k.v. to the neck for recurrent glandular involvement. She was followed in the Memorial Hospital, New York City, for one year where she received additional roentgen therapy (2,700 r) and was returned to the Boston Dispensary for further care on May 17, 1946. On November 15, 1946, she received deep x-ray therapy, 200 k.v., in two doses delivered to the left axilla, a total of 1,000 r. In January, 1947, roentgen evidence of mediastinal involvement was found. Additional therapy (2,700 r) was given to the mediastinal area in February, 1947. This was followed in April, 1947, with 1,100 r to the lumbosacral and left axillary regions. She remained quiescent in her remission and became pregnant for the first time in April, 1947. In view of the deep x-ray therapy over the lumbosacral area unwittingly administered at the same time that conception occurred, it was felt that continuation of the gestation was not advisable. A dilatation and curettage were therefore performed and a fetus of approximately eighty-five days of age was obtained. The endometrium was normal for pregnancy, the placental tissue normal, and there was little evidence of injury to the fetus. This patient has remained well up until the time of publication of this paper, six years after the onset of Hodgkin's disease, and is now six months post partum.

CASE 3.—B.D. No. 5093, Mrs. C. DeP., aged 23 years, was first seen in the Tumor Clinic of the Boston Dispensary on April 27, 1945, with a complaint of recent swelling of the glands in the neck. A biopsy revealed a patchy but striking eosinophilia, especially about the capsule, some monocytic infiltration in the same areas, occasional Reed-Sternberg cells, and areas of cellular deterioration and cytophagocytosis in the center of the nodule. In spite of some disagreement among pathologists, it was decided that this was Hodgkin's paraganuloma. Roentgen treatment to the involved areas was undertaken, and she received 1,200 r with the 200 k.v. machine in May, 1945. Her course was uneventful and the glands subsided after radiation. Because of recurrent enlargement of the nodes of the neck, she was offered 1,200 r again seven months later. Following an asymptomatic period of five months, 600 r were again applied to the neck. In August, 1946, she was found to have a two months' normal gestation. There were no unusual changes in her physical status, and the pregnancy proceeded normally until Feb. 25, 1947, at thirty-six weeks in her pregnancy, when she was admitted to the hospital for pelvic cramps and vaginal bleeding. A roentgen diagnosis of low placental implantation (? previa) was made. She was discharged after one week and returned to the hospital one month later with moderately severe vaginal bleeding and the absence of fetal heart tones. She went into labor and delivered naturally an apparently normal stillborn

TABLE I. REVIEW OF LITERATURE ON

NO.	YEAR	NO. OF CASES	AUTHOR	AGE AT ONSET	GRAVIDITY AT ONSET	DURATION OF PREGNANCY AND/OR HODGKIN'S DISEASE	INTERRUPTION OF GESTATION
1.	1911	1	Davis, A. B. ¹	32	v	Hodgkin's disease onset at 6 months' gestation	No
2.	1923	1	Gemmell, A. A. ²	23	ii	Hodgkin's disease onset at 4½ months' gestation 1½ years later	No No
3.	1926	1	Priesel, A., and Winkelbauer, A. ³	31	iii	2 years later Hodgkin's disease onset in first trimester	No No
4.	1934	5	Herz, A. ⁴	?	?	Hodgkin's disease onset early post partum	No
				?	?	Hodgkin's disease onset "shortly" after parturition	No
				?	?	Hodgkin's disease onset "before" parturition	No
				?	?	Hodgkin's disease onset "long before" gestation	No
				?	?	Hodgkin's disease onset at 9 years of age	No
5.	1934	1	Luetkens ⁵	?	?	?	No
6.	1938	1	von Braitenberg, H. ⁶	29	?	Hodgkin's disease onset 1 month post partum	No
7.	1939	1	Horster, H. ⁷	22	i	Pregnancy in 4th year of Hodgkin's disease 2nd pregnancy in 6th year of Hodgkin's disease	No Yes
8.	1940	2	Adair, F. L. ⁸	24	ii	Hodgkin's disease onset 3 years before gestation 2 years after abortion above 2 years after delivery above	No No Yes
				22	i	Hodgkin's disease onset 7 years before gestation	No
9.	1940	1	Parade, G. W. ⁹	22	i	Hodgkin's disease onset 2 years before gestation	No
10.	1940	2	Blitz ¹⁰	?	?	Hodgkin's disease onset "before" gestation	Yes
				?	?	Hodgkin's disease onset "before" gestation	Yes
11.	1941	1	Kushner, J. I. ¹¹	27	ii	Hodgkin's disease onset 16 months before gestation	No
12.	1942	1	Parade, G. W. ¹²	31	iv	Hodgkin's disease onset in 1st trimester of gestation	No
13.	1942	1	Klawans, A. H. ¹³	33	i	Hodgkin's disease onset at 24 weeks of gestation	No
14.	1945	5	Palacios Costa, N., Chavanne, F. C., and Zebel Fernández, O. ¹⁴	22	iv	Hodgkin's disease onset at 6th month of gestation	No
				20	i	Hodgkin's disease onset "before" gestation	No
				27	i	Hodgkin's disease onset at 4th month of gestation	No
				30	v	Hodgkin's disease onset at 5th month of gestation	No
				23	i	Hodgkin's disease onset at 4th month of gestation	No

the average survival period to be 3.4 years in women and 2.3 years in men. He stated that 92 per cent of women with Hodgkin's disease between the ages of 30 to 50 years survive three or more years.

It is of possible significance that Hodgkin's disease has not yet been reported in pregnancy before the age of 20 years nor beyond 39 years of age, although the disease itself tends to show a progressive rise in incidence up to 60 years of age.²⁴ The incidence of pregnancy is greatest between 20 and 30 years of age, and this fact would account for the fifteen cases reported in this age period out of a total of twenty-four cases in which age is stated. There is apparently no significance in the relations of the age of the patient, Hodgkin's disease, and pregnancy.

Information sufficient to establish the number of pregnancies is available in twenty-three of the twenty-nine cases reported. Analysis of the number of pregnancies in the reported patients reveals that 44 per cent (ten) were primigravida, 35 per cent (eight) were gravida ii, and 4 per cent (one) were gravida iii, 9 per cent gravida iv, and 9 per cent gravida v. There are thus 10 primi- and 13 multigravidous women in whom parity is reported. The incidence of the Hodgkin's disease in the 13 women who have had more than one gestation out of a total of 23 does not appear to lend weight to the theory of Gemmell that ovarian hyperactivity as indicated by the increased ovarian activity in pregnancy acts as a strong deterrent to Hodgkin's disease.

Consideration of the onset of Hodgkin's disease with relation to pregnancy reveals that sixteen of the twenty-nine cases in which adequate information is available reported the discovery of Hodgkin's disease after the diagnosis of pregnancy had been made. It is, of course, likely that the process antedated gestation in some if not all of these thirteen cases. This fact appears to be in accordance with the findings of Desjardin²⁵ who reported that estrogens had little or no effect on the course of Hodgkin's disease, especially in the light of the 55 per cent of the total number reported who dated their onset during gestation.

The pregnancies were permitted to terminate spontaneously in thirty-two gestations of a total of forty-two pregnancies in twenty-nine patients. In only seven reported patients, including one personal case, was the pregnancy interrupted before viability of the fetus because of the presence of Hodgkin's disease. Only Blitz (two cases) and Perrier (two cases) carried out this procedure in more than one instance. In none of these cases did the therapeutic abortion result in exacerbation of the Hodgkin's process. In our own case the patient has remained in a state of remission since her abortion six months ago.

Two women had three pregnancies, four had two pregnancies after the diagnosis of Hodgkin's disease had been made. The largest number, twenty-eight of thirty, cases at term, had a normal spontaneous delivery. There were but three spontaneous abortions apparently unrelated to the process. One patient had labor induced medically in the last trimester and one was delivered by cesarean section because of massive edema of the vulvar tissues. There is little evidence that spontaneous abortion occurs with significantly increased frequency in Hodgkin's disease. There is as well no evidence that acute intra- or postpartum hemorrhage occurs with increased incidence during Hodgkin's disease. In fact, uterine bleeding is rare in Hodgkin's disease. The labors are apparently normal in onset, duration, course, and termination, except in the one case that came to cesarean section because of excessive vulvar edema which may have been related to the lymphogranulomatosis. The puerperium was apparently normal in all instances from an obstetric standpoint. In no case was toxemia of pregnancy reported.

In three cases the fetus was involved in the maternal Hodgkin's disease at birth. A rather heated controversy has been aired in the German literature concerning the transmission of Hodgkin's disease across the placenta to the fetus.

TABLE

NO.	YEAR	NO. OF CASES	AUTHOR	AGE AT ONSET	GRAVID- ITY AT ONSET	DURATION OF PREGNANCY AND/OR HODGKIN'S DISEASE	INTER- RUPTION OF GESTA- TION
15.	1945	5	Perrier, H. ¹⁵	31	ii	Hodgkin's disease onset 8 years before gestation	No
				37	i	Hodgkin's disease onset 8 months before gestation	No
				39	ii	Hodgkin's disease onset 4 years before gestation	No
						4½ years after gestation above	Yes
				29	ii	Hodgkin's disease onset 1 year before gestation	Yes
						1½ years after gestation above	No
				38	ii	Hodgkin's disease onset 2 years before gestation	No
16.	1948	3	Kasdon, S. C.	29	i	Hodgkin's disease onset 1 month before gestation	No
						6 months after above	Yes
				26	i	Hodgkin's disease onset 5½ years before gestation	Yes
				24	ii	Hodgkin's disease onset 14 months before gestation	No

Priesel and Winkelbauer reported the occurrence of Hodgkin's disease in a 4½-month-old child, histologically verified, in whom the mother had a histologic diagnosis of Hodgkin's disease as well. Although the midwife in retrospect many months later reported many nodelike elevations in the placenta, no study of the placenta was made. A second child is reported by von Braitenberg with signs of Hodgkin's disease first appearing at one month of age. He suggested the possibility of transmission of the disease from mother to child across the placenta. However, there is no clear evidence that Hodgkin's disease was present in the mother and no pathologic changes were noted in the placenta. Leutkens reported a case of Hodgkin's disease in a child 33 months old, whose mother died of this process at two months post partum. Nevertheless, all thirty remaining viable children (91 per cent) born of mothers with Hodgkin's disease have not been reported to have developed it later on. It is of interest that a possible case of accidental laboratory transmission of Hodgkin's disease has been reported by Horder.³³

A normal child of 12 years is the oldest reported in the literature²⁶ born of a mother with Hodgkin's disease. In no case was there any evidence of placental involvement in the process. In no instance, as well, was there any evidence of damage to the fetus because of the use of roentgen radiation in the course of pregnancy. Adequate shielding of the fetus was used, of course, in all instances where roentgen rays were employed.

Analysis of the literature from the standpoint of the effect of the gestation and parturition on the disease is of special interest. In all, 40 pregnancies in 29 patients are available for study. Of these, 18 cases showed definite exacerbation of the Hodgkin's disease process during or immediately following the pregnancy. Thirteen of these occurred post partum and five ante partum. In 22 cases (55 per cent) neither pregnancy nor delivery resulted in an exacerbation. In view of the relatively short expectancy of life reported for women with Hodgkin's disease, this essentially equal incidence of exacerbations and remissions in the disease might be considered to be entirely due to chance. In any

HODGKIN'S DISEASE DURING PREGNANCY

MODE OF DELIVERY	COURSE AND OUTCOME OF HODGKIN'S DISEASE	RECOMMENDATION
Natural at term	Severe exacerbation during pregnancy. Died 119 days post partum	None
Natural at term	No effect on Hodgkin's disease	
Post-influenzal abortion 3½ months	No effect on Hodgkin's disease	Interruption advised when Hodgkin's disease found in early gestation. No interference advocated late in pregnancy
Natural at term	No effect on Hodgkin's disease	
Natural at term	Exacerbation post partum, death "shortly" afterwards. Post-mortem reported	None
? Natural at term	Exacerbation post partum for 4 months, then remission	
? Natural at term	Exacerbation post partum for 6 months, then remission	
? Natural at term	Exacerbation post partum, then remission for 1 year	Interruption early in gestation advised
? Natural at term	Exacerbation post partum	
? Natural at term	Exacerbation intrapartum following remission of many years	
? Natural at term	Exacerbation post partum, died in 3 months. Child developed Hodgkin's disease at 33 months	Interruption early in gestation advised
Natural at term	Exacerbation post partum, died "shortly" after. Postmortem reported	None
Natural at term	Exacerbation post partum	Interruption early in gestation advised
Vaginal hysterotomy at 4 months	No exacerbation following abortion	
Spontaneous abortion 1st trimester	No effect	
Natural at term	No effect	Interruption of gestation suggested
Abdominal hysterotomy, 26 weeks	No effect	
Natural at term	No effect	
Natural at term	Exacerbation post partum, died in 4 months	Interruption of gestation not advised
Abortion at 3 months	Exacerbation early in gestation	
Abortion, 1st trimester	Exacerbation early in gestation	Interruption of gestation advised
Natural at term	No effect. Died 2 years post partum. Postmortem examination reported	Interruption of gestation not advised
Natural at term	Exacerbation post partum, died in 9 days. Postmortem examination reported	See above
Cesarean section at term for edema of vulva	No effect	Interruption of gestation not advised
Natural at term	Exacerbation post partum, died in 15 days	
Natural at term	No effect	
Natural at term	Exacerbation post partum	Interruption of gestation not advised
Natural at term	No effect	
Natural (?) at term	No effect	

would tend to lend some weight to the theory that the ovarian hyperactivity present in gestation acts as an inhibitor of Hodgkin's disease, and must be considered in the light of the evidence to the contrary presented earlier in this paper. It must be noted that in two cases of the seven where pregnancy was terminated by interference before viability of the fetus, it is possible to establish the survival period following the interruption of the pregnancy. It is impossible to draw definite conclusions from this meager material concerning the value of interruption of pregnancy for extending the survival time for women with Hodgkin's disease. It appears most likely that maternal survival is not significantly altered by early interruption of the gestation.

Consideration of the effect of early previable interruption of pregnancy upon the course of Hodgkin's disease is of major interest. Blitz reported two patients in whom interruption of the pregnancy was effected because of an exacerbation of the Hodgkin's disease in the first trimester of pregnancy. In both rapid remissions in the process obtained followed interference. Perrier reported the earliest exacerbation three months following previable interruption of the pregnancy. In no case did an acute exacerbation of the lymphogranulomatosis occur directly following induced abortion. This can be compared with the postpartum exacerbations occurring in thirteen of thirty-two cases (41 per cent) which went to term and were delivered. It appears likely from this consideration that exacerbations in the course of Hodgkin's disease are much more prone to follow delivery at term than delivery previally.

Only the case reports of Davis, Kushner, von Braitenberg, and Parade present postmortem examinations in the parturients. In none of these patients was there reported involvement of the ovaries or uterus in lymphogranulomatosis.

The recommendations offered in the management of pregnancy during Hodgkin's disease are available from eleven of the fifteen authors who have presented cases. Opinions are equally divided with six advising interruption of the pregnancy and five against interference in the course of gestation. It must be realized that in all cases these expressions of opinion are attitudes which are impossible to establish on a firm footing. Gemmell stated that the diagnosis of Hodgkin's disease early in pregnancy is indication for interruption. On the other hand, he felt that the reaction to early interruption of pregnancy would likely be as bad in advanced Hodgkin's disease as that at term. This is not substantiated by our analysis. He quotes several other British authors, such as Murray²⁸ in Albutt and Rolleston's *System of Medicine* that "parturition has . . . an unfavorable influence upon the progress of the disease." Gowers²⁹ is also quoted from Reynold's *System of Medicine* that "in one case only (of 25 fatal female cases) did the disease apparently commence during pregnancy. The progress of the disease was, in another, distinctly checked during pregnancy and it advanced rapidly after delivery." Dyes³⁰ felt that the response to x-ray therapy should determine the indication for interruption and that conservation of the fetus is advisable whenever possible. Parade felt that although the process may be aggravated by pregnancy, interruption should, nevertheless, not be advised routinely. The desire of the parents for the child plays an important part in the management of the pregnancy in his opinion, as in that of Herz. However, such humanistic considerations, intensely significant as they may be in practice, should play little part in the factual consideration of the intereffects of Hodgkin's disease and pregnancy. Perrier states that "there do not exist, in general, medical indications to interrupt a pregnancy in the course of lymphogranulomatosis." Gilbert³¹ offered five cases of pregnancy out of thirty women reported with lymphogranulomatosis. Insufficient material is presented in all cases, however, for analysis. He states that remissions are uncomplicated after x-ray therapy for Hodgkin's disease during pregnancy. He feels that both marriage and pregnancy are to be discouraged in the presence of Hodgkin's

I—CONT'D

MODE OF DELIVERY	COURSE AND OUTCOME OF HODGKIN'S DISEASE	RECOMMENDATION
Natural at term	No effect	
Natural at term	Exacerbation post partum	
Natural at term	No effect	
Interruption, 1st trimester	No effect, died 3 years post partum	Interruption of pregnancy not advised
Interruption, 1st trimester	No effect	
Natural at term	No effect. Exacerbation 3 months post partum, died at 6 months	
Natural at term	No effect on course. Died 5 years post partum	
Spontaneous abortion	No effect	
Induction of labor 34-36 weeks of gestation	Rapid progression of Hodgkin's disease through gestation with death 8 days' post partum	See summary and conclusions of this report
Abortion at 3 months	No effect	
Spontaneous at term	No effect	

case, the evidence from this standpoint is certainly not strong that Hodgkin's disease is activated by pregnancy. It would, of course, be of great value to know the incidence and frequency of exacerbations in a nine-month period in a comparable group of nonpregnant patients in order to state more clearly whether exacerbations in Hodgkin's disease occur with greater frequency during pregnancy. Craver²⁷ states he would expect a 50 per cent incidence of exacerbations in a nine-month period in non-pregnant Hodgkin's patients of this type.

TABLE II. DURATION OF LIFE POST PARTUM IN HODGKIN'S DISEASE FOR PATIENTS IN WHOM DEATH IS REPORTED IN THE LITERATURE

AUTHOR	YEAR	WEEKS
1. Davis ¹	1911	17
2. Priesel and Winkelbauer ³	1926	"shortly after delivery"
3. Luetkens ⁵	1934	22
4. von Braitenberg ⁶	1938	"shortly after delivery"
5. Parade ⁹	1940	29
6. Parade ¹²	1942	1
7. Palacios Costa, Chavanne and Zebel Fernández ¹⁴	1945	2
8. Perrier ¹⁵	1945	156
9. Perrier ¹⁵	1945	26
10. Perrier ¹⁵	1945	364
11. Kasdon	1948	1

Table II presents the time after delivery in which death occurred in the eleven cases in which this evidence is available. The longest period of survival after delivery in which death is reported is seven years, and the shortest period is eight days. In no case did death occur before evacuation of the uterus. This would appear to be of great significance since one would ordinarily expect some of the twenty-nine patients to terminate their course fatally, but this has not yet been reported during the antenatal period in Hodgkin's disease. This evidence

Of greatest significance is the evidence which can be applied to the establishment of an attitude which will determine the management of pregnancy in Hodgkin's disease. In view of the fact that exacerbations in the process occurred in but eighteen of forty-two gestations during Hodgkin's disease, it is felt that this is little more than the incidence of exacerbations in Hodgkin's disease which one would expect without pregnancy in a comparable group of women. Of the eighteen patients who developed exacerbations during the gestational and puerperal period, thirteen occurred after parturition. This is of real but as yet undetermined significance, especially in the light of the freedom from exacerbations in all patients in whom interruption of their pregnancies, either spontaneously or by induction, occurred before term. It is therefore felt that pregnancy has no demonstrable effect on the over-all incidence of exacerbations in Hodgkin's disease. If there is any tendency whatsoever for exacerbations in Hodgkin's disease to occur during pregnancy, they most likely follow delivery at term. It is therefore considered that there is little evidence from this study to advocate interruption of pregnancy during the course of Hodgkin's disease. When specific and definite obstetrical indications for interruption of pregnancy not related to the Hodgkin's process are present, there is certainly no contraindication to interruption of pregnancy as far as the Hodgkin's disease is concerned.

On the other hand, Hodgkin's disease has little or no effect on the occurrence, course, duration, complications, or end results of gestation.

Conclusions

1. Hodgkin's disease complicating pregnancy does not grossly affect ovulation, fertility, incidence of spontaneous abortion, ante-, intra-, or postpartum hemorrhage.
2. The obstetric aspects of gestation, parturition, and the puerperium are not affected by coincidental Hodgkin's disease.
3. Hodgkin's disease is transmitted from the mother to the fetus across the placenta in 9 per cent of reported cases.
4. There is no report in the literature of injury to the shielded fetus from roentgen radiation used in the treatment of Hodgkin's disease.
5. Interruption of pregnancy during the course of Hodgkin's disease is not indicated from the evidence at hand.

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disease. However, if pregnancy occurs during a remission of the disease, he does not advise interruption of the gestation. A "wait and see" attitude best expresses his position.

Summary

A review and analysis of the available published literature on Hodgkin's disease and pregnancy with a report of three cases are presented. The need for such a study is clearly indicated by the complete absence of comprehensive information in the modern literature.

It is obvious from the reports of the multiple gestations during Hodgkin's disease that fertility is not grossly affected by the process. Spontaneous abortion, contrary to earlier statements, is also apparently unrelated to the presence of Hodgkin's disease in the light of but three occurrences in forty gestations. Hemorrhages occurring ante, intra, or post partum show no increased incidence in Hodgkin's disease. In spite of evidence to the contrary, there is considerable doubt that estrogens play a significant part in either the onset or severity of Hodgkin's disease.

Study of the age incidence reveals little of significance. The youngest patient was 20 years and the oldest 39 years of age, with an average of 28.3 years. There are 10 primi- and 16 multigravidous women. In sixteen of the twenty-nine cases in which sufficient information can be obtained, pregnancy occurred after the onset of lymphogranulomatosis. It is probable that the disease was present in some, if not in all, of the remaining cases before gestation developed. There does not appear to be any interference with ovulation or fertility by Hodgkin's disease from this fact alone, in contrast to the aberrations in ovarian activity which have been reported in leucemia.³²

In all, thirty-two of a total of forty-two gestations were delivered at term. There were seven interruptions of pregnancy before viability of the fetus, and three spontaneous abortions which were not considered to be related to the lymphogranulomatosis. The largest number, twenty-eight of thirty, delivered naturally and spontaneously at term. One patient was induced medically, and one patient was delivered by cesarean section because of excessive vulvar edema. The latter indication for hysterotomy may have been related to the presence of Hodgkin's disease, but is an exceedingly rare complication in a rare complication of pregnancy. The problem of placental transmission of Hodgkin's disease to the fetus should be considered as a possibility. Of the three reported instances of Hodgkin's disease in young infants, the diagnosis of Hodgkin's disease is unquestioned in two of the mothers. On the other hand, all other viable children born of mothers with Hodgkin's disease have been found to be free of the disease. It can be stated that Hodgkin's disease is transmitted from the mother to the fetus across the placenta in 9 per cent of reported cases. Lymphogranulomatosis has not been reported in the placenta or membranes.

Adequate shielding has prevented the occurrence of radiation injury to the fetus in all cases where roentgen therapy was employed in exacerbations of Hodgkin's disease. Thus far there have been no reports of pregnancy in Hodgkin's disease treated with nitrogen mustards. Evaluation of this new therapeutic tool in the management of lymphogranulomatosis must await further study.

INDICATIONS FOR HORMONAL PELLETS IN THE THERAPY OF ENDOCRINE AND GYNECIC DISORDERS*

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IT HAD been noted by many investigators in both animal and clinical experimentation that implantation of hard compressed pellets of crystalline steroids resulted in a slow and more physiologic absorption of the hormone than that observed after parenteral administration. Since the amount of the hormone released to the organism is continuous though minute in quantity, it is conceivable that by this method the endogenous mechanism of hormonal secretion is more nearly approached and the physiologic action of the hormone more closely imitated.¹⁻⁶ In 1942 Corner⁷ predicted that, "pellets will probably be used in human cases in which long continued action is required, not only because of the continuous absorption, but also because insertion of the pellet, which can be done through a hollow needle, avoids repeated hypodermic punctures."

The numerous objections to the repeated parenteral administration of hormonal preparations are apparent to both physician and patient. The implantation of hormonal pellets may be undertaken in a great variety of conditions requiring prolonged hormonal therapy. Besides eliminating the necessity and inconvenience of frequent injections, the economy of this mode of therapy places it within reach of most patients. Satisfactory results may be obtained for periods up to six months and longer.

Technique of Pellet Injection

With the use of the Kearns Pellet Injector (Fig. 1), the disadvantages of previous methods of subcutaneous and subfascial pellet implantation have been largely eliminated. Implantation by these earlier methods was followed by expulsion of the pellet in as many as 15 per cent of cases, whereas, with the Kearns instrument pellet extrusion is rarely seen, and in our experience, occurred in less than 2 per cent. In those instances in which the pellets were recovered after varied periods, and weighed, it was found that absorption closely followed the more or less constant curves previously reported.^{8, 9}

An area of skin is chosen on the anterior abdominal wall about one inch medial to the anterior superior spine of the iliac crest, on either the right or left side. The skin is cleansed with any of the accepted antiseptic preparations, and then anesthetized with 1 or 2 c.c. of a 2 per cent solution of procaine hydrochloride (Fig. 2). The sterilized pellet injector with stylet in place is directed parallel to the inguinal ligament, and inserted subcutaneously to the depth of the first bolt (Fig. 3). The stylet is removed, and the pellet placed in the groove at the exposed end of the hollow needle. Care should be taken when placing

*This work was aided by a grant from Schering Corporation, Bloomfield, N. J. Supplies of pellets of estradiol, testosterone (Orton-P), progesterone, and desoxycorticosterone acetate (Cortate) were made available through the courtesy of Dr. W. H. Stoner and Dr. Edward Henderson of Schering Corporation.

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the pellet into the cannula, as the pellet cannot be re-sterilized if it falls out and becomes contaminated. By holding the sterile tray beneath the groove, the pellet will be caught in this tray, and can be replaced (Fig. 4). As many pellets as indicated may be added. Twelve pellets have been implanted by a single injection. The blunt plunger is then fully inserted, gently pushing the pellets into the subcutaneous tissues. The instrument is withdrawn, and a dry dressing placed over the wound. The pellets may be palpated in the subcutaneous tissues of the anterior abdominal wall, just above the middle of Poupart's ligament.

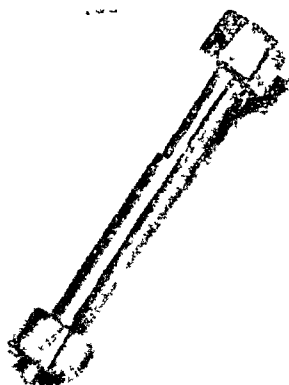


Fig. 3.

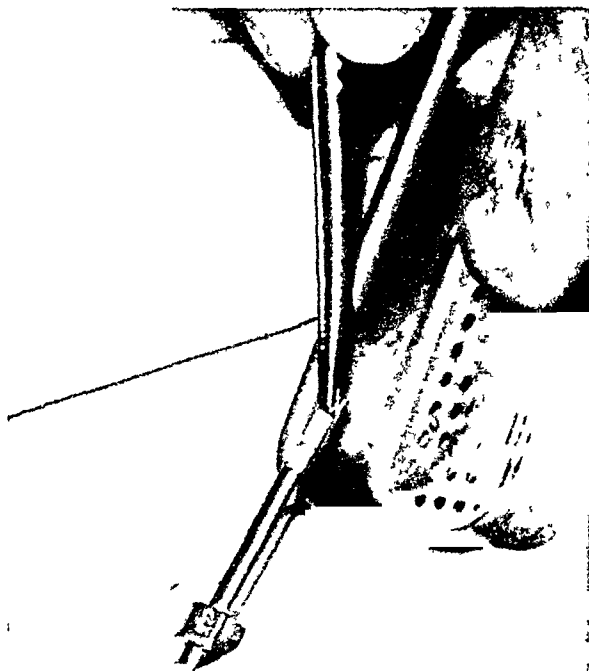


Fig. 4.

Fig. 3.—Subcutaneous insertion of the cannula with stylet.

Fig. 4.—Introduction of the pellets into the groove at the exposed end of the cannula.

Absorption

If pellets are manufactured under standard conditions, i.e., uniformly compressed crystalline material, it holds that pellets of greater weight will be of proportionately greater size. The rate of absorption, per pellet, will depend on its surface area. The percentage of absorption of each weight group of pellets will follow its own definite curve. The total rate of absorption on any given day or any given time depends on the number of pellets implanted and not on the actual weight of the pellets. Since pellets of similar size are more or less absorbed at moderately uniform rates, and since the rate of absorption depends on the number of pellets and the surface area, the following hypothesis may be in order: "The rate of absorption of any given amount of crystalline hormone depends on the number of pellets implanted at one time and not on the size or weight of the pellets, and the time that the



Fig. 1.—The Kearns Pellet Injector (unassembled) with pellet.

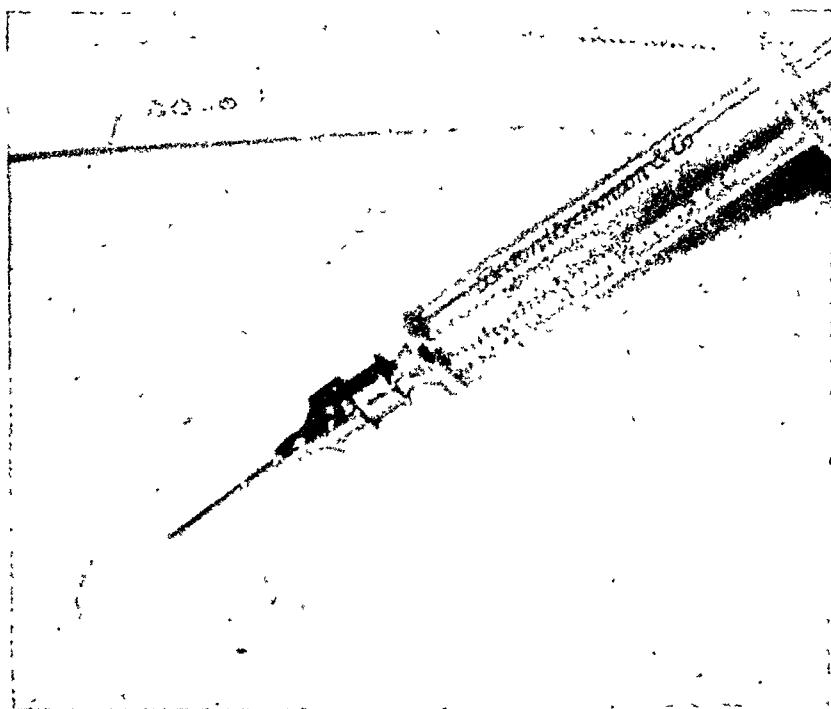


Fig. 2.—Anesthetizing the skin with procaine hydrochloride solution.

ceeding month, the curve tending to level after the hundredth day. The decrease in rate of absorption is inversely proportional to the surface of the pellet. Fig. 5 shows the percentage mean absorption curve for 100 mg. pellets of testosterone propionate.⁸ Fig. 6 shows the percentage absorption of 50 mg. pellets of progesterone.⁹

Indications for the Use of Pellets

Estradiol Pellets (25 mg. in weight).—

1. In patients with severe menopausal syndrome in whom prolonged injections of estrogens are necessary.
2. In young women with hypoplasia of uterus or breasts.
3. Dysmenorrhea associated with hypoplasia of the uterus.

Note: Estradiol pellets are contraindicated in patients with a history of cancer or with so-called precancerous lesions. It is preferable that estradiol pellets should not be used except in those patients without uteri.

Progesterone Pellets (50 mg. in weight).—

1. May be used along with estrogens in the treatment of menopausal patients.
2. In selected patients with nervous tension states.
3. Nymphomaniacal tendencies that prove distressing.
4. In treatment of habitual abortion.¹¹
5. In treatment of puberal breast hypertrophy.⁹

Note: Combined estradiol-progesterone pellet implantation should never be used in the menopausal patient with an intact uterus, as prolonged bleeding usually ensues.

Testosterone Pellets (75 mg. in weight).—

1. In certain patients with symptoms of menopausal syndrome in whom estrogen therapy has proved unsatisfactory or is contraindicated.
2. In combination with estradiol pellets in patients with uteri who have severe menopausal symptoms, in order to prevent the untoward bleeding induced by estrogens.¹²
3. The dysmenorrheic patient with possible endometriosis or small fibroids.
4. The patient with fibromyomata for whom surgery is not feasible.
5. The patient with nocturia of endocrine origin.¹³
6. The female who is not psychologically frigid and in whom increased libido is desirable.¹⁴
7. As a palliative measure in patients with advanced carcinoma of the breast.
8. In combination with desoxycorticosterone pellets for Addison's disease.

Note: Testosterone pellets should not be used in women who have a tendency toward acne or hirsutism.

Desoxycorticosterone Acetate Pellets (75 mg. in weight).—

1. Addison's disease.¹⁵
2. In panhypopituitarism, pellets of desoxycorticosterone acetate may be implanted along with testosterone.
3. In certain asthenic patients who have low blood pressure, low blood sugar, and marked fatigability, it appears that this form of medication proves helpful.

Note: Desoxycorticosterone is contraindicated in hypertension or heart disease.

Typical Case Reports

Climacteric.—

(1) *Estradiol Pellets:* D. E., a 56-year-old white woman, was seen in April, 1947. Hysterectomy had been performed in 1936. During the preceding seven years, the patient

pellets continue to give off appreciable material depends on the size and weight of the pellets implanted.¹⁰ The manner of absorption is mainly a physical phenomenon depending on the surface area exposed to the dissolving action of tissue fluids. Influencing factors are the density of the pellet, the size of the particles (crystals) that comprise the pellet, and the site of implantation.⁸

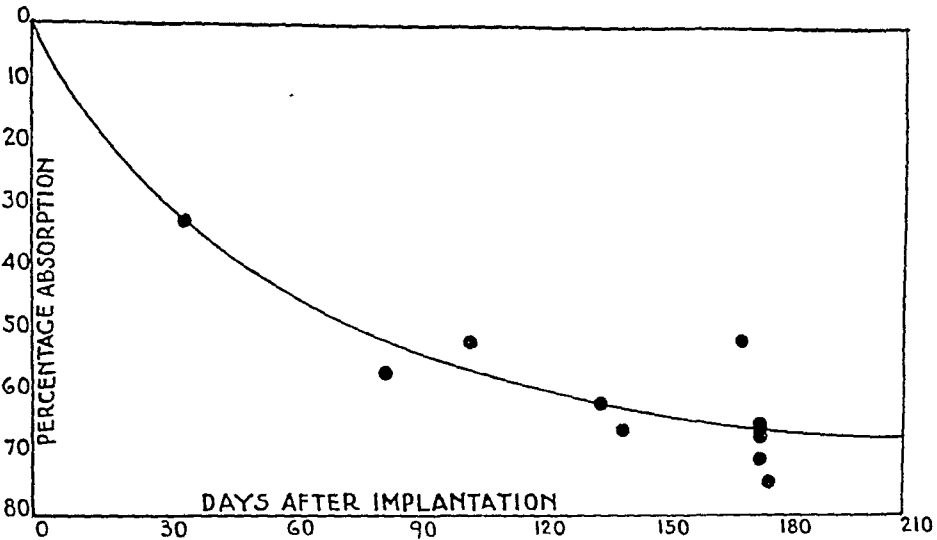


Fig. 5.—Percentage mean absorption curve for 100 mg. pellets of testosterone propionate. (From: Greenblatt, R. B., and Hair, L. Q.: *J. Clin. Endocrinol.* 2: 315, 1942.)

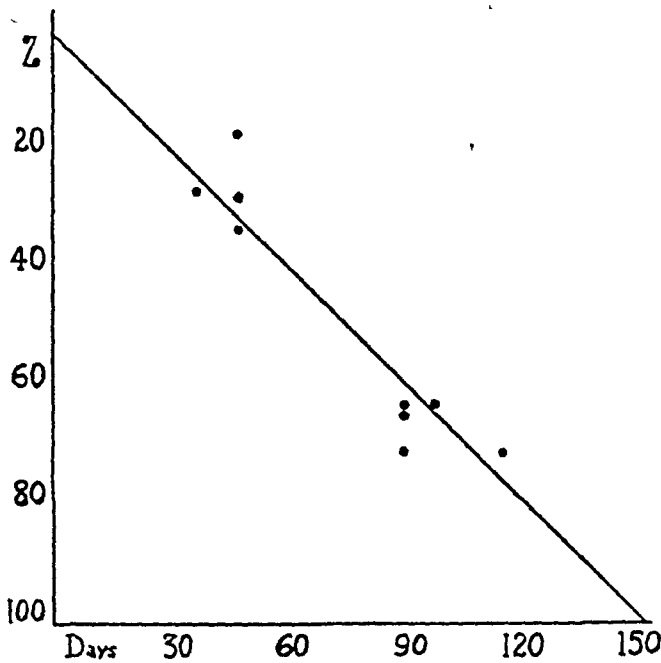


Fig. 6.—Percentage absorption of 50 mg. pellets of progesterone. (From: Greenblatt, R. B., and Hair, L. Q.: *J. Clin. Endocrinol.* 5: 38, 1945.)

When the percentage absorption is plotted against the number of days that the pellets remain in situ, the resultant curves are more or less smooth with the individual deviations of each weight group being only moderate in extent. The percentage of absorption during the first month is relatively rapid for all groups. The rate of absorption progressively decreases with each suc-

She was seen again August 22, and stated that her condition was greatly improved. Headaches had ceased, she slept well, and her libido was definitely increased. Examination showed the clitoris to be slightly enlarged, and very sensitive. The patient returned March 11, 1947, and stated that symptoms had been adequately controlled for seven months, but recently her well-being and libido had lessened. Two 75 mg. pellets of testosterone were again implanted. There was immediate improvement, and her complaints were controlled for an additional period of five months. She was seen on Sept. 19, 1947, complaining of a recent decrease in libido. Two 75 mg. pellets of testosterone were implanted. Libido was restored, and remained at a high level for five months. She was last seen on Jan. 24, 1948, at which time one 25 mg. pellet of estradiol, and one 75 mg. pellet of testosterone were implanted in order to maintain her well-being and clinical improvement.

Endometriosis.—

Testosterone Pellets: E. S., a 24-year-old white woman, complained of dysmenorrhea for the duration of the menses so severe that her physician had to resort to some opiate for relief. Following the cessation of flow, pain in the left side persisted for one week afterward. Examination revealed a retroverted adherent uterus, with tenderness and some fullness of the left fornix. A diagnosis was made of endometriosis. In 1943, complete relief was afforded for a period of six months by injections of testosterone propionate, 25 mg. every fifth day. Two months after the injections were discontinued, the pain returned. Therapy was resumed, and continued for eight months with amelioration of her syndrome. In April, 1946, the patient complained of excruciating pain in the left side for one week following menstruation. She had noticed burning on urination when the pain was present. The patient stated that she was relieved of the dysmenorrhea. At this time urologic consultation was sought, and the urologist concurred in the diagnosis of endometriosis. It was felt that the pain was produced by an endometrioma causing pressure on the ureter. Three 75 mg. pellets of testosterone were implanted. The pain was relieved for six months, but recurred following the next menstrual period. Pelvic examination showed the uterus still retroverted, but slightly more moveable. There was tenderness in the left fornix; and some induration of the left uterosacral ligament. Three 75 mg. pellets of testosterone were again implanted. There was no pain following menstruation in December. The patient became pregnant, but aborted in February, 1947. Shortly thereafter, she became pregnant again, and was delivered on Nov. 29, 1947, of a normal male infant.

Addison's Disease.—

Desoxycorticosterone and Testosterone Pellets: R. C., a 31-year-old white nullipara, was first seen in September, 1946. Her complaints were extreme weakness, headaches, marked generalized pigmentation especially of face and upper extremities, and partial loss of head, axillary, and pubic hair. The diagnosis of Addison's disease was confirmed by laboratory tests. At this time three 75 mg. pellets of desoxycorticosterone were implanted. Aqueous adrenal cortical extract was prescribed in 1 c.c. doses twice weekly. Extra salt was added to the diet. During the following three months the patient improved rapidly. On Dec. 12, 1946, one 75 mg. pellet of desoxycorticosterone was implanted. Improvement continued, and in May, 1947, three 75 mg. pellets of desoxycorticosterone, and two 75 mg. pellets of testosterone were implanted. The patient continued to do well. She gained weight, did not fatigue easily, hair growth was restored, and pigmentation decreased somewhat. On Aug. 12, 1947, one 75 mg. pellet of desoxycorticosterone, and one 75 mg. pellet of testosterone were implanted. The patient was last seen on Feb. 4, 1948. At this time she stated that she had not taken any adrenal cortical extract or extra salt for the past four months, and that she felt extremely well.

Summary

The implantation of hormonal pellets has proved of value in the management of a great variety of endocrine and gynecic disorders. Pellet implantation is indicated in those conditions where prolonged hormonal therapy appears necessary. With the use of the Kearns Pellet Injector, pellet implantation is a simple office procedure. Some of the indications and contraindications

had frequent hot flushes, cried easily, was unable to concentrate, and stated that her memory was poor. Her emotions were easily disturbed. She had received repeated courses of estrogen therapy, orally and parenterally, with only partial alleviation of symptoms. In April, 1947, two 25 mg. pellets of estradiol were implanted. Improvement was noted almost immediately. The hot flushes were practically eliminated. Her emotions stabilized, she was more receptive to visitors, and her attitude to life in general was greatly improved. Her symptoms have remained under control for a period of ten months.

(2) *Estradiol and Testosterone Pellets:* B. B., a 50-year-old white woman, was first seen Aug. 22, 1942, complaining of frequent, severe hot flushes, nocturia, nervousness, backache, headaches, and paresthesia. Menses had ceased three years previously. During the following five years the patient was treated with estrogens, progestogens, and androgens, given orally and parenterally, with unsatisfactory results. On October 6, 1947, the patient's complaints were particularly severe. At this time two 25 mg. pellets of estradiol, and one 75 mg. pellet of testosterone were implanted. Improvement was noted shortly. She experienced almost complete relief of all symptoms, and her complaints have been satisfactorily controlled during the six months' follow-up to date. No untoward bleeding occurred.

(3) *Estradiol, Progesterone, and Testosterone Pellets:* B. J., a white woman aged 41 years, was seen on Nov. 14, 1946. Her uterus, tubes, and ovaries had been surgically removed in 1939. The patient complained of fatigue, emotional instability with nervousness, and extreme depression, formication, and occasional hot flushes. She was treated with oral estrogens for several weeks, and showed some improvement. On Jan. 13, 1947, one 25 mg. pellet of estradiol, one 50 mg. pellet of progesterone, and one 75 mg. pellet of testosterone were implanted. She was seen the following month and stated that her symptoms were completely ameliorated. The symptoms remained under control for six months. On July 3, 1947, the patient returned, and reported that there was a decline in her well-being. One 25 mg. pellet of estradiol, and one 75 mg. pellet of testosterone were implanted. She remained in good health during the next six months, but noted somewhat less improvement than following the first series of pellets. She returned on Jan. 9, 1948, because some of her symptoms were becoming manifest, however slight. She feared a recurrence, and requested a repeat implantation. One 25 mg. pellet of estradiol, one 50 mg. pellet of progesterone, and one 75 mg. pellet of testosterone were again implanted. Her complaints were again quickly relieved, and she has remained in good health to date.

Habitual Abortion.—

Estradiol and Progesterone Pellets: J. W., a gravida v, para i, white woman aged 43 years of age, was seen June 5, 1946, with a history of three abortions following the birth of her first child in 1936. Each abortion occurred between the second and third months of gestation. She also had one abortion prior to the first child. At the time of her visit, the period was approximately one week overdue, the date of the last menstrual period being April 28. Examination suggested pregnancy, and the pregnancy test was reported positive. Two 25 mg. pellets of estradiol, and three 50 mg. pellets of progesterone were implanted. The patient was kept at bed rest until the seventh month of gestation. Thyroid and vitamin E were prescribed. During the fifth, sixth, and early part of the seventh months, 5 mg. of progesterone were given by injection twice weekly. At no time during the course of pregnancy was there any evidence of threatening abortion. The patient was delivered of a normal, 7¼ lb. female infant on Jan. 30, 1947.

Loss of Libido.—

Testosterone Pellets.—G. P., a white female of 31 years was seen on May 30, 1946. She had been married for 12 years, but had no children. She complained of nervousness, backache, severe headaches, insomnia, and swelling of feet and ankles. She had not menstruated during the preceding year, although previously the menses had been regular. Her libido was markedly diminished. Examination revealed an infantile uterus. Suction curettage was performed, and the endometrium was atrophic. The vaginal smear showed mostly basal cells. A diagnosis was made of precocious menopause, with marked reduction of libido. The patient was treated with stilbestrol, thyroid, and vitamin B for three weeks, with only slight improvement. On July 11, 1946, two 75 mg. pellets of testosterone were implanted.

MORPHINE SUPPRESSION OF URINARY OUTPUT IN PREGNANT AND NONPREGNANT WOMEN

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THE effect of morphine on urinary output has been a controversial subject¹⁻⁴ as indicated in a review of the literature by Ferrier and Sokoloff.⁵ These authors presented evidence of the antidiuretic action of morphine and Demerol in patients with congestive heart failure. In 1944 and 1945, the antidiuretic effect of morphine in dogs was described by DeBodo,^{6, 7} who concluded that this effect was due to release of antidiuretic principle from the neurohypophysis. In further experiments, it was shown that phenobarbital, Sodium Amytal and pentobarbital also had this antidiuretic effect but to a lesser degree, depending upon the dosage given.

The studies here presented began in May, 1947, shortly after an apparent suppression of urinary output was noted following the administration of morphine to several patients with eclampsia or severe pre-eclampsia. It was decided to determine the effect of a single injection of morphine on the urinary output of normal pregnant and nonpregnant women.

Method

The pregnant patients were in the last trimester of uncomplicated pregnancies. The nonpregnant individuals had entered the hospital because of uncomplicated vaginal prolapse, sterility, or for sterilization. Various age groups were represented. Most of the studies were carried out before operation but a few were done after the seventh day of a normal afebrile postoperative convalescence.

During the evening before the first experimental day, the patient was instructed to drink at least 500 c.c. of water before midnight. Thereafter, she took nothing by mouth for the next sixteen hours. At 8 A.M., an indwelling catheter was inserted and the urine obtained was discarded. An intravenous infusion of 2,400 c.c. of 5 per cent dextrose in distilled water was begun and the rate of flow regulated so that this volume would be administered during a five-hour period. The urine was collected as eight consecutive hourly specimens from 9 A.M. until 4 P.M. The next sixteen-hour output was collected as a single specimen except for the initial series of nine patients from whom only the eight hourly specimens were obtained. During this sixteen-hour period the patient was offered a full liquid diet.

The procedure was duplicated on a control day and a test day with at least forty-eight hours intervening. The only variable between the two days was the injection of morphine on the test day. In three instances the morphine day preceded the control day. The morphine sulphate, $\frac{1}{4}$ grain (16 mg.), was given intramuscularly at the time the intravenous fluid was started. In a few patients, less than 2,400 c.c. of fluid was given intravenously; however, the fluids were

for pellet implantation are listed. A number of typical case reports are cited in which pellet implantation was of definite benefit to the patient. It appears that the pellet method of hormone administration has more nearly approached the endogenous rate of hormonal secretion. Furthermore, its use has made possible a clearer understanding of the physiologic properties of certain steroids.

Testosterone and desoxycorticosterone acetate pellets are now commercially available, and it is hoped that pellets of estradiol and progesterone will soon be made available for general use.

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The hematocrit readings done at 8 A.M. and 4 P.M. on each test day showed no evidence of any blood dilution. This would indicate that the retained fluids were extravascular. Blood pressures and pulse rates were recorded every hour for eight hours but the average values and the deviations were not significantly different on the two days.

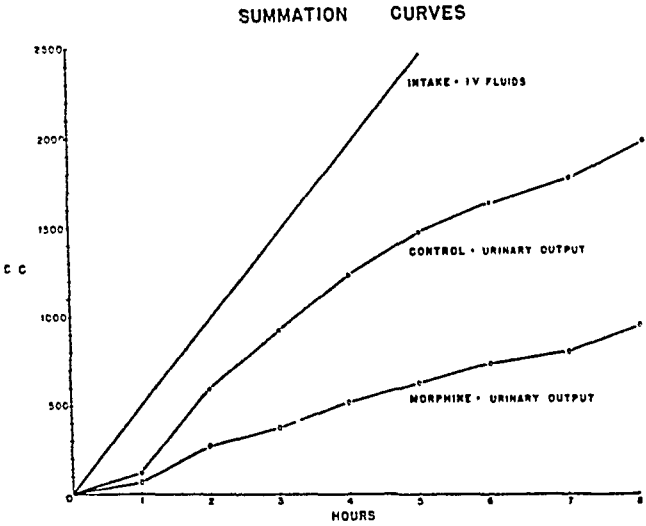


Fig. 1.—Summation curves of the average eight-hour urinary outputs obtained on nine women. 2,400 c.c. 5 per cent dextrose were given intravenously at a constant rate over five hours. On morphine day, morphine sulfate, $\frac{1}{4}$ grain (16 mg.), was given intramuscularly at the start of the infusion.

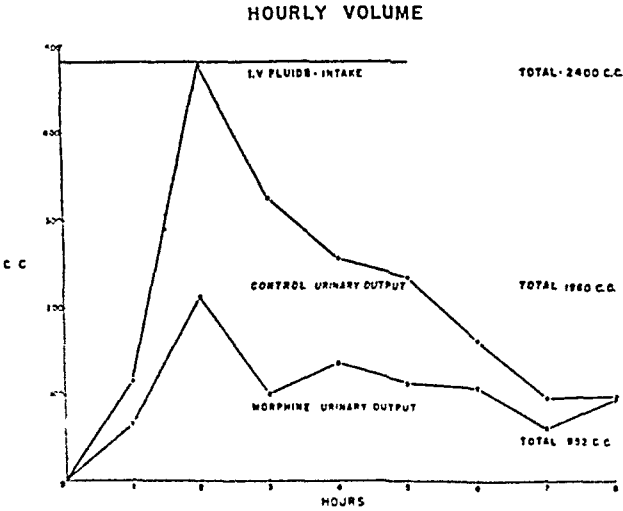


Fig. 2.—Average hourly urine volumes on same group of nine women as are represented in Fig. 1.

Urinary chloride concentrations were determined on each of the eight hourly specimens and the sixteen-hour specimen. The total chloride was calculated for each specimen and for the total twenty-four hours. The results, expressed as grams of sodium chloride, are shown in Table II and in Figs. 3 to 6. In four of the six patients, there was a definite decrease in total urinary chlorides on the morphine day. The concentration of chloride in the urine was not consistently increased on the morphine days as compared to the control days. Thus the low concentration of chloride together with the decreased urinary volume resulted in a decreased total chloride output on the morphine

carefully measured and the same volume at approximately the same rate was given on the next test day. Thus, while volumes varied slightly, the volume and rate of intake in the same patient were equal on both days.

Only the urine volume and specific gravity were noted on the first nine patients. In a second group of six normal patients, four pregnant and two non-pregnant, the urine was collected over the twenty-four hour period as described. In addition, hematocrit determinations were made at the beginning and end of the initial eight-hour period. Blood pressures and pulse rates were recorded hourly for eight hours beginning at 8 A.M. on the experimental day. In addition to volume and specific gravity, determinations of chloride concentration were also made for each of the nine specimens.

The preliminary chloride intake was that of the general hospital diet which contains 4 to 5 Gm. of sodium chloride daily. The full liquid diet contained 5 to 6 Gm. of sodium chloride per day.

In a few patients who reacted to the infusion with chills and fever, the experiment was discontinued and the record discarded. Occasionally, nausea and vomiting necessitated discontinuing the infusion late in its course. In most instances, the emesis volume was accurately measured and included in the output volume.

Observations

The results obtained on the initial group of nine patients are shown in Table I. In all instances, the injection of morphine caused a decrease in urinary volume. In two cases, the total eight-hour urinary excretion was not appreciably diminished but hourly output was diminished during the maximal clinical effect of the morphine, with a compensatory increase during the last two or three hours.

The average summation curves for all the patients in this group are shown in Fig. 1. The total eight-hour urine output on the morphine days averaged 48 per cent of that on the control days. In Fig. 2, the average hourly output is represented. It is interesting to note that the increased urine volume during the first hours of the infusion was followed by a decreasing output even though fluid intake continued at a constant rate.

TABLE I. NORMAL WOMEN ARE REPRESENTED. THE TOTAL EIGHT-HOUR URINARY VOLUME FOR THE CONTROL PERIOD IS COMPARED WITH THE VOLUME OBTAINED AFTER INJECTION OF $\frac{1}{4}$ GRAIN (16 MG.) MORPHINE SULPHATE

PATIENT	AGE	WEIGHT IN LBS.	TOTAL OUTPUT IN C.C.	
			CONTROL DAY	MORPHINE DAY
I. J.	17	105	1965	1625
S. P.	26	154	1889	1633
M. D.	35	152	1980	523
P. G.	49	150	1160	722
E. H.	52	171	1905	351
C. R.	56	166	2145	1205
M. H.	61	152	2335	482
E. W.	61	177	1725	1005
A. K.	73	163	2540	1025
Average:			1960	952

Studies on the second group of patients were postponed until October, 1947, in order to avoid the hot summer months when insensible water loss might be excessive. In this group of six patients, the observations covered a twenty-four-hour period as previously described. The group included four pregnant women and two patients from the gynecologic service. In all instances, the urinary output was suppressed for eight hours on the morphine day but later there was a compensatory increase so that the total twenty-four-hour volume approached that of the control day. (Table II.)

days. The low chloride concentrations were correlated with comparably low specific gravities, indicating that the urinary solutes remained low even during the period of diminished urine volume.

This is contrary to the results obtained by DeBodo on dogs,⁷ in which he reported a fiftyfold increase in chloride concentration and a twofold increase in total chlorides excreted in the first three hours after giving morphine.

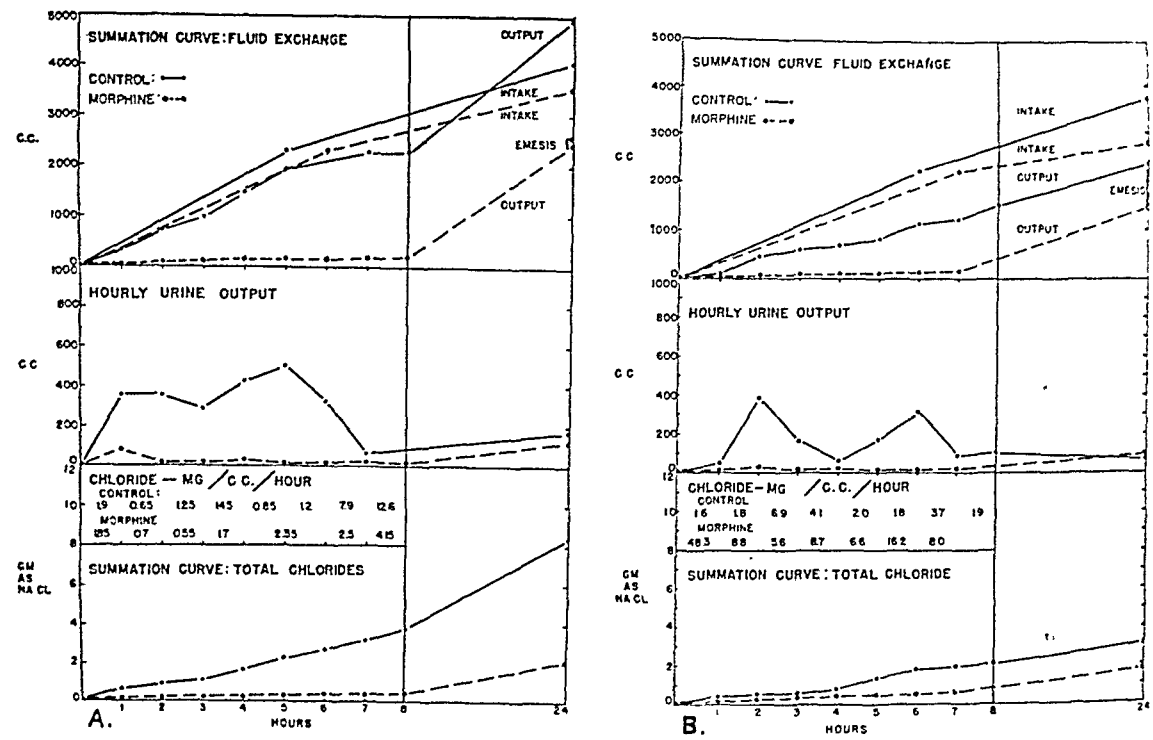


Fig. 4.—Graphic representation of the results obtained on two normal nonpregnant women observed under the same conditions as the pregnant patients represented in Fig. 3. A. E. S., aged 33 years. B. E. M., aged 29 years.

TABLE II. THE INTRAVENOUS FLUID VOLUME, TIME OF ADMINISTRATION, AND THE EFFECT OF MORPHINE OR PITRESSIN ON FLUID OUTPUT AND CHLORIDE EXCRETION IN PATIENTS SHOWN IN FIGS. 3, 4, AND 5

PATIENT	AGE	DAY	INTRAVENOUS 5 PER CENT DEXTROSE		URINE VOLUME IN C.C.		TOTAL CHLORIDES IN GM.
			TOTAL C.C.	TIME HR.	8 HR.	24 HR.	
Normal Pregnant Women in Third Trimester							
R. M.	27	Control	2300	4½	1821	3671	5.5
		Morphine	2300	4½	1312	3332	3.7
B. V.	18	Control	2400	5½	2141	3091	4.2
		Morphine	2400	5½	1050	2285	4.7
G. W.	32	Control	1400	3	938	3678	4.4
		Morphine	1400	3	273	1683	3.2
M. B.	19	Control	1350	3½	1064	1495	2.2
		Morphine	1350	3½	615	1378	1.2
		2 units Pitresin (H)	1100	3¼	1155	2025	5.2
Normal Nonpregnant Women							
E. M.	29	Control	2200	6½	1297	2337	3.0
		Morphine	2200	6½	65	2165	1.0
E. S.	33	Control	2300	5½	2352	4952	8.4
		Morphine	2300	5½	209	2401	2.0
M. S.	19	Control	2400	5	2915	3088	7.0
		0.5 c.c. Pitresin tannate in oil	2400	5	813	1623	10.7

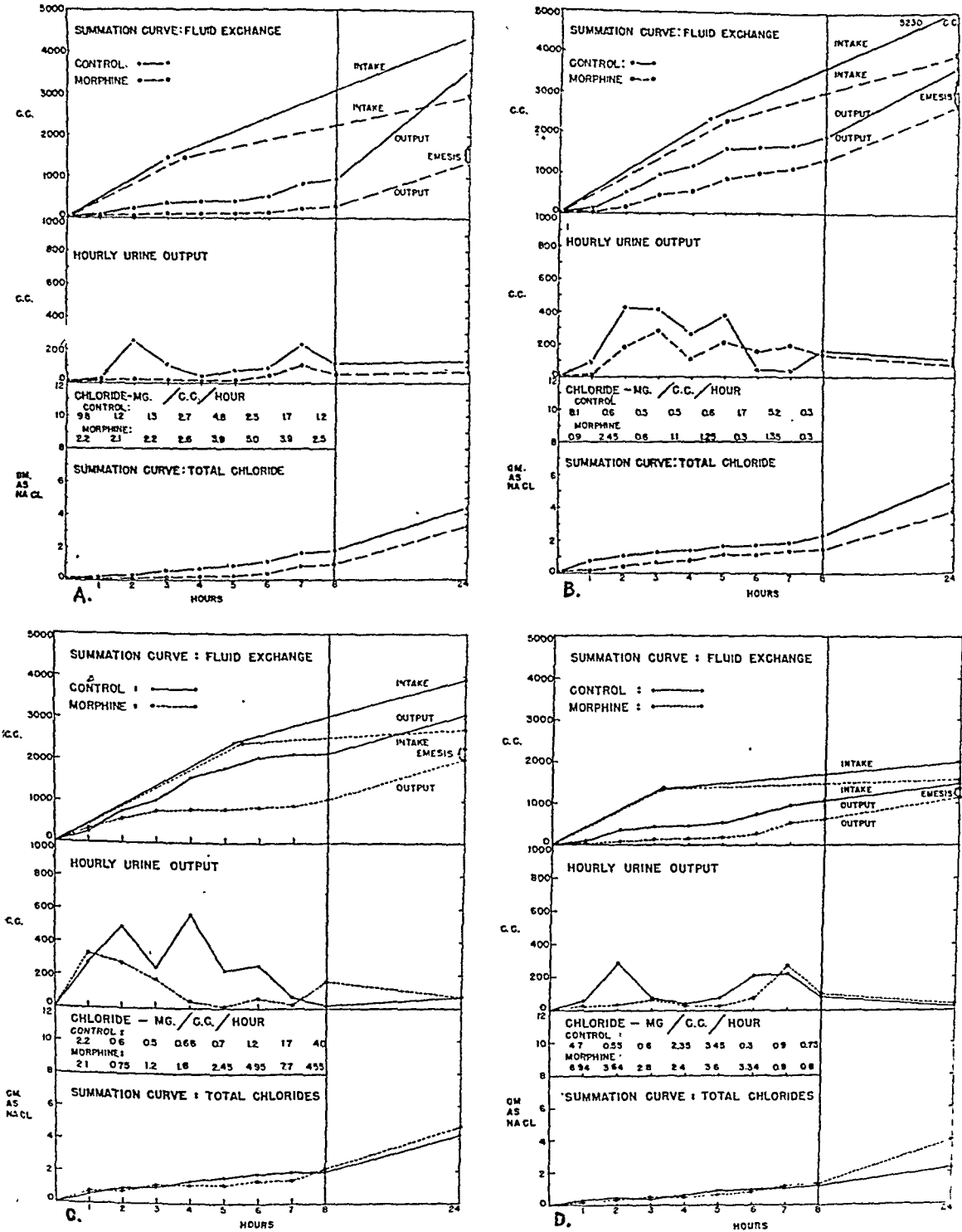


Fig. 3.—Graphic representation of results obtained on four normal pregnant women. Hourly urine specimens were collected for the first eight hours and a single specimen for the next sixteen hours. Fluid exchange is represented as intravenous and oral intake against urinary output. The insert represents chloride concentration in each of the first eight hourly specimens. A. G. W., aged 32 years, seven months pregnant. B. R. M., aged 27 years, seven and one-half months pregnant. C. B. V., aged 18 years, seven months pregnant. D. M. B., aged 19 years, six and one-half months pregnant.

Further observations were believed necessary to determine whether the release of posterior pituitary hormone is the cause of the antidiuretic effect of morphine. After DeBodo had determined the action of morphine in dogs, he injected Pitressin into normal animals and noted a marked similarity in the results. This was the next step in our observations on the human being.

In two patients, injections of Pitressin were substituted for morphine in order to compare their antidiuretic action. One patient (M. B., aged 19 years), in the third trimester of a normal pregnancy, was given 2 units of aqueous Pitressin, while the other (M. S., aged 19 years) received 5 units of Pitressin tannate in oil.

The patient receiving the aqueous Pitressin demonstrated little suppression of urine output except during the first three hours following the injection. (Fig. 5A.) However, the urinary chloride concentration increased markedly and total twenty-four-hour chloride output was increased from 4.0 Gm. (on control day) to 5.27 Gm. The same patient on a morphine day (Fig. 3D) had urinary suppression and also showed a decrease of total chlorides to 2.2 Gm. as compared to 4.0 Gm. on control day.

The second patient (Fig. 5B), who was given Pitressin tannate in oil, had marked suppression of urinary output over the entire twenty-four-hour period as compared with the control day. However, in spite of the urine suppression, the chloride concentration on the Pitressin day was so high that the total chloride output was 10.8 Gm. as compared to 7.0 Gm.

The results obtained with injection of Pitressin in human beings confirmed the findings in dogs. However, the similar action of Pitressin and morphine in dogs could not be demonstrated in women.

DeBodo also presented the results of morphine given to dogs with diabetes insipidus (stalk-sectioned). He found that the antidiuretic action of morphine was abolished in this group. While it is not possible to determine the exact amount of posterior pituitary still functioning in patients with diabetes insipidus, these individuals offer the only means of comparison with the stalk-sectioned laboratory animal. Two patients with diabetes insipidus were observed, using the same methods as with the normal control groups. The diabetes insipidus was confirmed in both patients before any test days were observed. (See Appendix.)

The urine outputs of the two patients with diabetes insipidus (Figs. 6A and 6B) were suppressed on the morphine day but to a lesser degree than in most of the normal patients. In patient L. B., the chloride concentration and total chloride output during the first eight hours was approximately the same on the two days. The total chloride excretion on the morphine day increased slightly over that of the control day in the subsequent sixteen-hour specimen. In patient M. D., the urinary chloride concentration and the total chlorides were decreased during the morphine test.

These observations thus demonstrated a urinary suppression caused by morphine in two patients with long-standing diabetes insipidus. Since this suppression occurred in spite of reduced output of the antidiuretic principle of the posterior pituitary, it appears that the action of morphine is not mediated by the antidiuretic hormone. This is additional evidence that the effect observed by DeBodo is not the same as that which occurs in human beings.

Discussion

The one constant result obtained in this series of observations was the suppression of urinary output after a single injection of morphine. The degree of suppression varied from patient to patient, with the age factor appearing to be most important. In general, the younger the patient, the less the suppression. This was probably due to the degree of tolerance to morphine. The

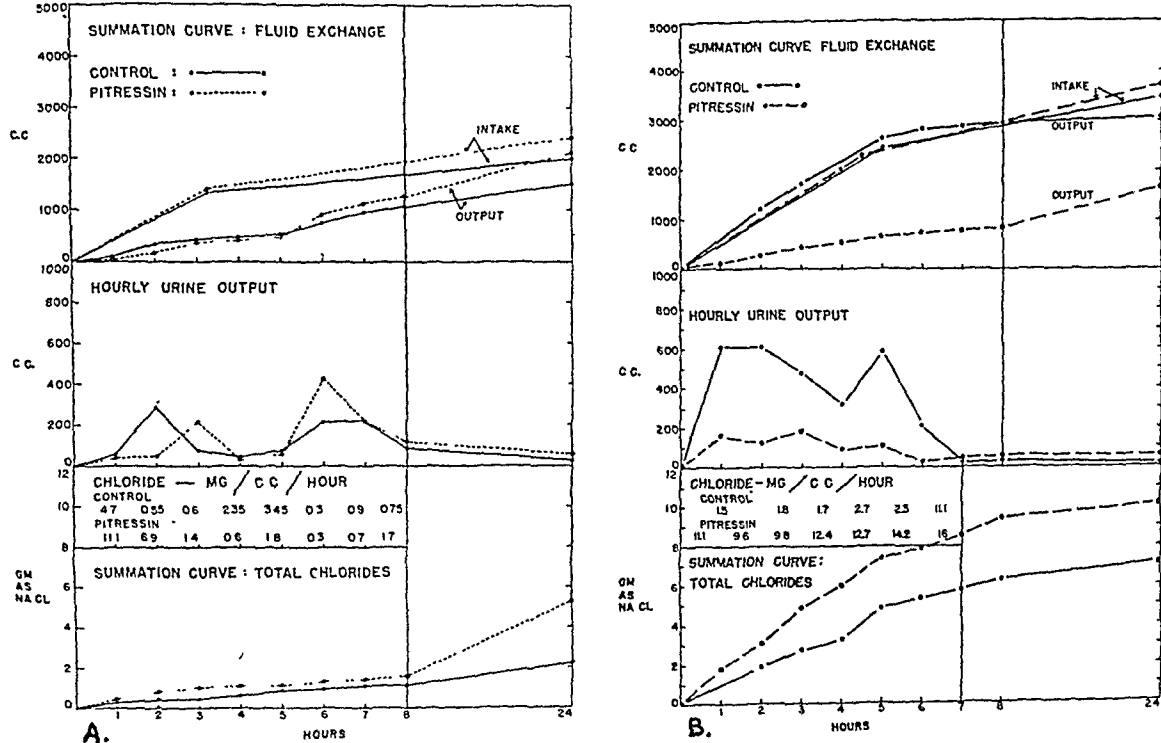


Fig. 5.—Graphic representation of the results obtained on two women, one pregnant, who were given Pitressin instead of morphine and the results are compared with the control day. A. M. B., aged 19 years, six and one-half months pregnant. Patient given 2 units aqueous Pitressin at 8 A.M. Compared with Fig. 3D which represents effect of morphine on the same patient. B. M. S., aged 19 years. Patient given 5 units of Pitressin tannate in oil at 8 A.M.

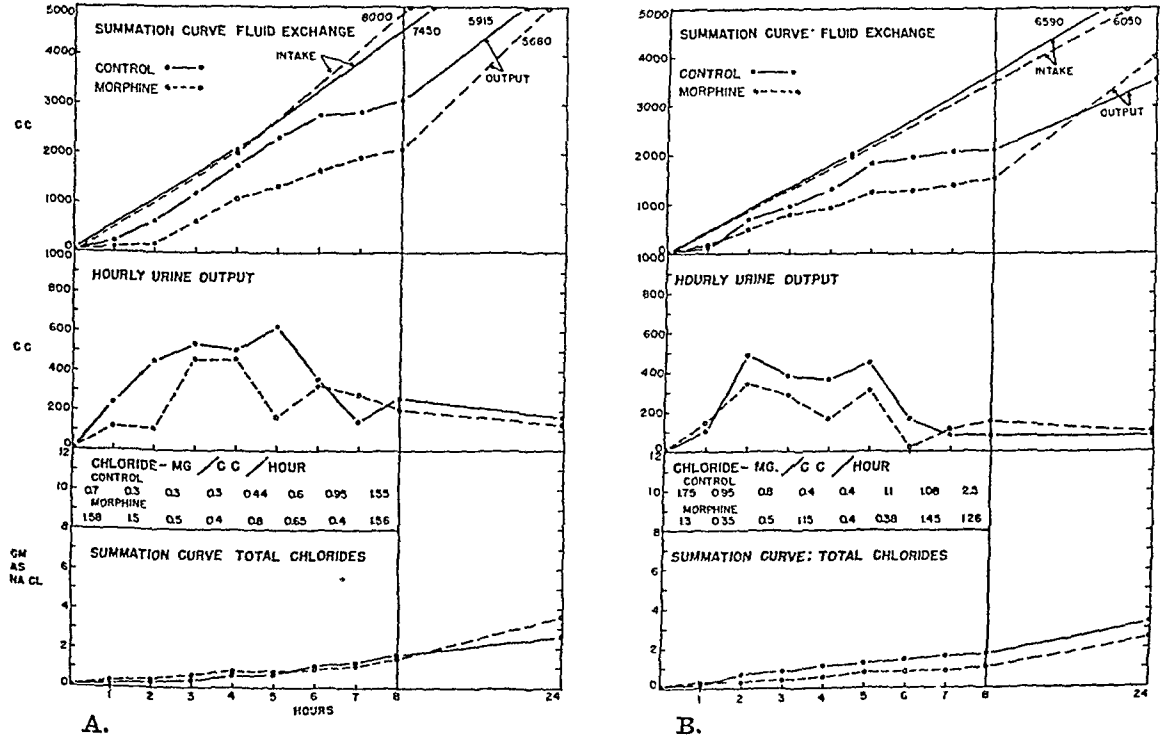


Fig. 6.—Graphic representation of the effect of morphine in two women with diabetes insipidus presented for comparison with its effect on normal women, Figs. 3, 4, and 5. A. L. B., aged 26 years. B. M. D., aged 62 years.

interpret the results. Their findings on four normal control patients showed an increase of total urinary chlorides in two instances but the morphine negated the effect of the mercurial in the other two. In the patients with cardiac failure, the total urinary chlorides remained the same or decreased. The decrease in urinary output was not a constant finding. In none of our normal patients was the total urinary chloride markedly increased and usually there was a depression following morphine.

Summary

1. Eleven normal nonpregnant and four normal pregnant women and two patients with diabetes insipidus were given intravenous infusions of 5 per cent dextrose and their urinary outputs were measured for twenty-four hours. After several days, the procedure was repeated with the patient receiving morphine sulphate, $\frac{1}{4}$ grain (16 mg.), intramuscularly at the time the intravenous infusion was begun. The results obtained on the control day were compared with those obtained on the morphine day.

2. During the intravenous administration of 5 per cent dextrose at a constant rate over a five-hour period in normal subjects, there is an initial diuresis in the first two hours followed by a decrease in urinary output.

3. A single dose of morphine caused a suppression of urinary output which tended to eliminate the initial diuretic surge normally seen in the first two hours. This was a constant effect but varied in degree.

4. On morphine test days, as compared with control days, there was no increase of specific gravity or chloride concentration of the urine. Hematocrit determinations taken before the infusion and again eight hours later were unchanged during both control and morphine days.

5. Two patients, one pregnant, were given single injections of Pitressin. There was an increased concentration of urinary chlorides and an increase in total chlorides. One patient had suppression of urinary output and the other showed an output about equal to that on the control day.

6. Two patients with diabetes insipidus demonstrated suppression of urinary output when given morphine. In one instance the total chlorides were decreased and in the other they remained unchanged.

7. These observations suggest that the data from dog experiments, indicating that morphine causes a release of antidiuretic hormone from the neurohypophysis, cannot be accepted in explanation of the antidiuretic effect of morphine in normal women.

Appendix

The first patient (L. B., aged 26 years) had a history of diabetes insipidus for the past twelve years. She had been taking 1 c.c. Pitressin tannate in oil every one and one-half to two days since 1940. Thorough studies in 1940 and again on this admission revealed no other demonstrable abnormality.

The second patient (M. D., aged 62 years) had the diagnosis of diabetes insipidus made in 1941. She had been taking injections of 1 c.c. Pitressin tannate in oil every three to four days in order to control her symptoms.

In order to re-affirm the diagnosis of diabetes insipidus, the method of Carter and Robbins⁸ was used. This consists of an initial oral hydration period followed by the insertion of an indwelling catheter and the collection of two subsequent fifteen-minute urine

clinical narcotic effect of morphine was approximately the same in all age groups, but the younger patients recovered more rapidly. No attempt was made to regulate the dose of morphine in proportion to body weight, nor was the intravenous fluid intake so regulated. The purpose was to determine the effect of a single one-quarter-grain (16 mg.) injection of morphine, and the fluid (5 per cent dextrose) was given intravenously in approximately the rate and amount which might be used clinically.

Since it was not possible to control as many factors as DeBodo did in the dog, the only possible comparison involves the urinary output and the urinary chlorides. Our findings agree that suppression occurs, but neither the chloride concentration nor the total chloride output was elevated as found by DeBodo in dogs. In most instances the total chlorides were decreased. However, it must be pointed out that the doses of morphine used by DeBodo greatly exceeded those used on the human being in this series. It is not known what the effect of greater doses or repeated doses of morphine would be in the human subject.

In the two patients, one pregnant and one nonpregnant, who received Pitressin, there was a marked increase in urinary chloride concentration on the Pitressin day as compared with the control day. This result can be compared with the morphine day in the pregnant patients when there was a decrease of total chloride and in chloride concentration as compared with the control day. This again indicates that a mechanism other than the posterior pituitary is acting to cause urinary suppression.

In the two patients with long-standing diabetes insipidus, Pitressin injections were withheld until the symptoms of the disease entity had become re-established. In both patients, the urinary volumes were suppressed on the morphine day. The chloride concentration and the total urinary chlorides were about equal in one patient while both the concentration and total values decreased in the other. Again evidence was adduced pointing away from the mediation of the morphine effect through the neurohypophysis.

A finding, which was incidental to the main purpose of the experiments, but which evoked considerable interest, was the effect of the prolonged intravenous infusion of 5 per cent dextrose on the urinary output during control days. Little was found in the literature to explain why the initial diuretic surge during the first hours was followed by a rapid drop in output and a smaller secondary rise at about the fourth hour. This typical pattern can be seen on the figures showing the hourly urine outputs. The significance of this pattern is not known, but should be studied further. Verney,⁹ in discussing the antidiuretic hormone and its release in the dog, showed that intravenous hypertonic solutions of dextrose resulted in a release of antidiuretic substance and a drop in urinary output. "Osmoreceptors" present somewhere in the vascular beds of the internal carotid arteries are sensitive to osmotic pressure changes and can cause a release of antidiuretic hormone from the neurohypophysis. Whether a similar mechanism might be induced with prolonged intravenous administration of 5 per cent dextrose is yet to be determined.

Ferrier and Sokoloff reported an antidiuretic effect of morphine in congestive heart failure. The fact that their patients were given 3 Gm. of ammonium chloride daily and received a mercurial diuretic makes it difficult to

AN ELECTROPHORETIC STUDY OF MATERNAL, FETAL, AND INFANT SERA*

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MANY chemical and immunologic¹⁻⁹ and a few electrophoretic¹⁰⁻¹⁴ comparisons have been made of sera from several species throughout the life span. Scarcely any data have been reported for embryonic sera.^{4, 7, 15, 16} This paper reports studies on the changes in the electrophoretic patterns of maternal, fetal, and infant sera. The meaning of the patterns is discussed from the point of view of protein content, placental permeability, and species relationships. An attempt is made to correlate serum globulin content with the changes in antibody titer during the first few months of postnatal life.

Experimental

Blood was obtained from the umbilical cords of eight newborn infants (two were identical twins) and from their mothers soon after delivery. Blood was again taken by jugular vein from the same and other babies at various times during the first year. Samples of venous blood throughout the gestation period and at delivery were taken from mothers. Samples of blood were also taken from the hearts, up to the sixth month, of aborted or miscarried fetuses and from the umbilical cords of premature infants.

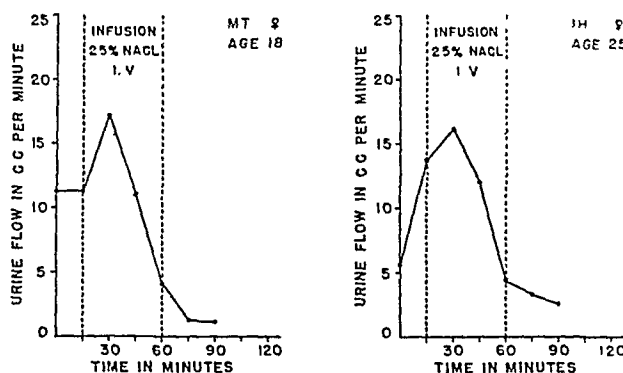
All of the analyses were made in a buffer 0.02 M with respect to sodium phosphate and 0.15 M with respect to sodium chloride (pH 7.4 and ionic strength 0.2).¹⁷ The samples of sera were diluted with 2 parts of this buffer. Three ml. of each of these diluted sera were dialyzed in viscose casings against one liter of the buffer for twenty hours, whereupon the volumes were remeasured in order to correct for any change in volume during dialysis. The conductivity and pH of both the diluted sera and the dialysate were routinely taken. The conductivities were used in calculating the mobilities of the various electrophoretic components.

The analyses were carried out in a Tiselius apparatus¹⁸ having a single-sectioned tall cell of 2 ml. capacity. The center section is 50 mm. tall, 15 mm. deep (along optic path) and each channel is 2 mm. wide. The channels are 10 mm. apart (center to center). Patterns obtained in this cell are indistinguishable after enlargement from those obtained in the standard 11 ml. Tiselius cell. A current of 18.7 Ma. flowed through the cell and produced a field strength of 6.5 volts/cm. All patterns were obtained by the scanning method of Longsworth,¹⁹ on panchromatic plates (Kodak M) the light source being a 200-watt tungsten projector lamp. Pencil tracings of five times magnified patterns were measured with a planimeter. The components were segregated by drawing perpendiculars to the base line according to the procedure of Tiselius and Kabat.¹⁷

*The authors wish to acknowledge the valuable interest and assistance in obtaining fetal and infant sera rendered by Dr. P. A. di Sant'Agnese of Babies Hospital and Drs. John Field and J. M. Greer of the Department of Obstetrics and Gynecology.

specimens to serve as controls. Intravenous infusion of 2.5 per cent sodium chloride was then given at the rate of 0.25 c.c. per kg. per minute over a period of 45 minutes. Urine was collected for each fifteen-minute interval during the infusion, and for 30 to 60 minutes after its conclusion. Aqueous Pitressin, 0.1 unit, was given intravenously to the diabetes insipidus patients thirty minutes after cessation of the infusion.

NORMAL SUBJECTS



DIABETES INSIPIDUS

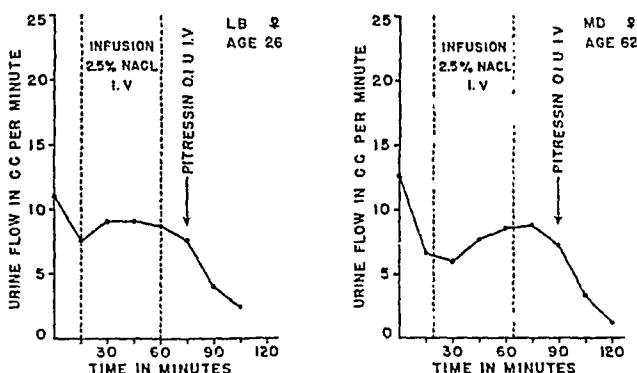


Fig. 7.—Graphic representation of the effect of intravenous hypertonic (2.5 per cent) sodium chloride solution on the urine output in normal women and in those with diabetes insipidus. This is the test of Carter and Robbins.⁸

Fig. 7 shows the results plotted in minute urine output. A typical diabetes insipidus curve was obtained on each of the test patients. This is characterized by the maintained or increased urine volume during the infusion of hypertonic saline, in contrast to the abrupt decrease in urine volume during the saline infusion in normal subjects (A. H. and M. T.). These control patients, aged 18 and 25 years, were on the gynecologic service awaiting sterilization.

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Results

The data on maternal, fetal, and infant sera covering the gestation period and ten months of postnatal life in the infant are presented in Tables I, II, III, and IV and the results are summarized in the chart of Fig. 2. It may be

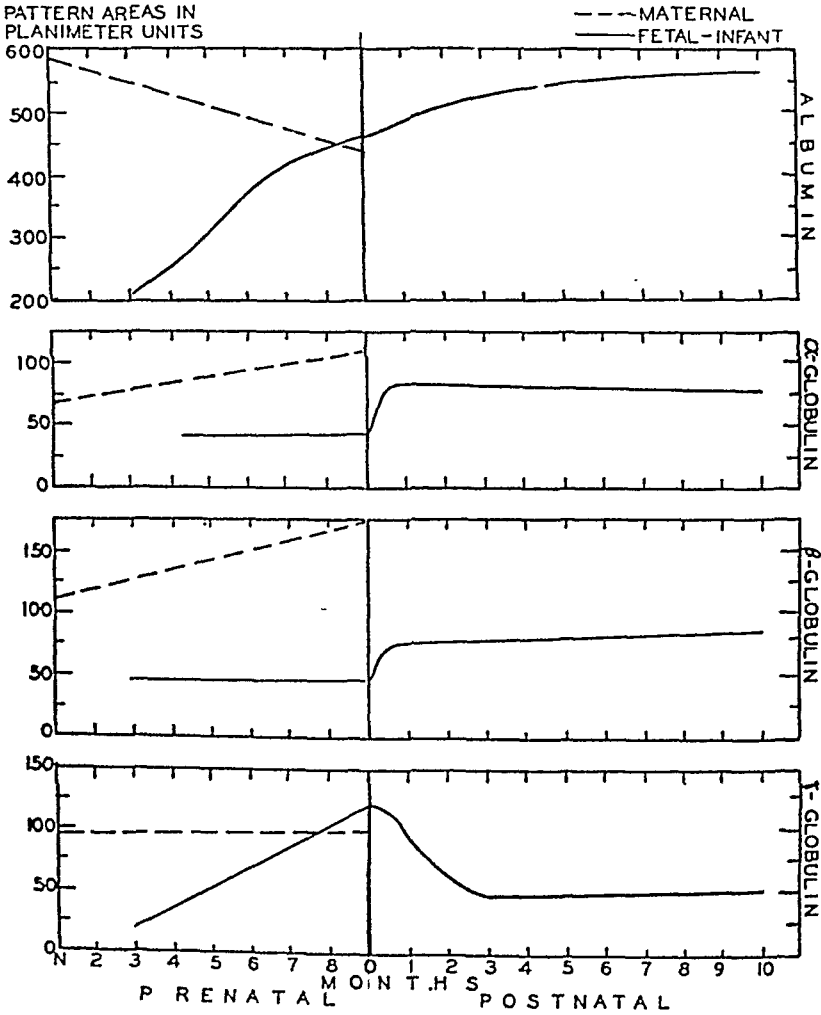


FIG. 2.—Chart indicating the development of serum proteins in the human fetus and during the first ten months of postnatal life. Changes in maternal serum during pregnancy are also shown.

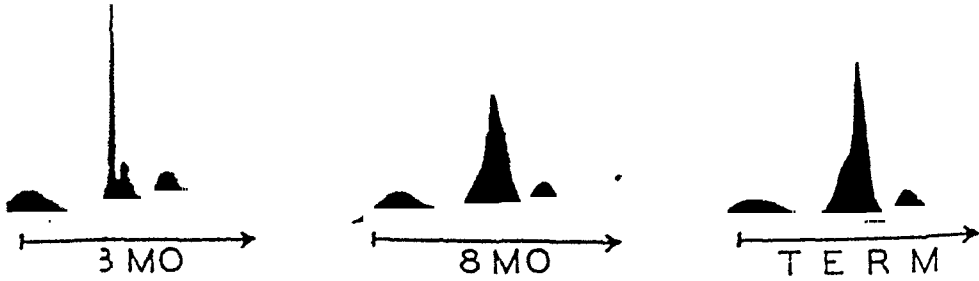


Fig. 3.—Pregnancy serum patterns

observed (Table I, Figs. 2 and 3) that the albumin of the maternal sera decreases during pregnancy, whereas alpha- and beta-globulins, particularly beta-globulin, increase greatly and gamma-globulin remains essentially unchanged.

Although most of the data on human serum found in the literature are given in grams per cent of protein calculated from nitrogen or density measurements, electrophoretic pattern areas were not converted into grams per 100 c.c. serum because the specific refraction increment* for each of the various electrophoretic components was not determined. The pattern area represents a composite of protein, lipid, and carbohydrate, all having different specific refractions and occurring in different concentrations in the various electrophoretic fractions.²⁰

Reiss,²¹ Robertson,²² Arnd and Hafner,²³ Starlinger and Hartl,²⁴ and Adair and Robinson²⁵ have reported that the specific refraction varied from 0.0017 to 0.0023 or greater for the various serum fractions. Similar variations have been found for electrophoretically separated fractions.²⁶ The variations are less if the values are calculated from dry-weight measurements. Nevertheless, they are appreciable because of the diversity of the constituents of the fractions.

Beside the errors introduced by the complexity of the serum composition, there are systemic errors in the moving boundary method which influence the pattern area. The inequality in concentration of buffer ions in the serum and its dialysate at Donnon equilibrium²⁴ and the delta- and epsilon-effects²⁷ which are dependent on the nature of the buffer and the ratio of the colloid to the crystalloid ions^{27, 28} give rise to boundary anomalies. These effects were reduced by diluting the samples with a buffer of high ionic strength.†

The delta- and epsilon-, especially the epsilon (descending) gradients are almost negligible in this phosphate-saline buffer. Analyses of sera or serum fractions containing no gamma-globulin or component of similar low mobility reveal epsilon-boundaries of extremely low areas, as is illustrated in Fig. 1. The rat serum pattern illustrated in Fig. 1A was taken from the top half of ultra-centrifuge tubes after prolonged centrifugation at 50,000 r.p.m. and is probably not entirely gamma-globulin-free. Normal chick (40 days old) serum (Fig. 1B) has no component of low mobility.

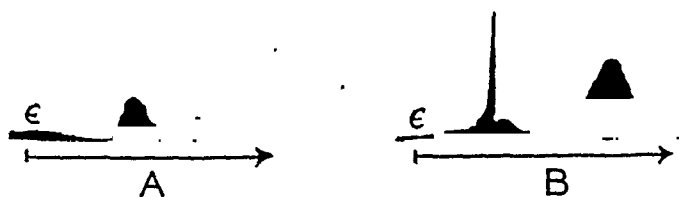


Fig. 1.—Electrophoresis patterns (from the descending limb) of γ -globulin-free rat serum (A) and chick serum (B) illustrating the low ϵ or salt boundary obtained in phosphate-saline buffer of ionic strength 0.2.

Some samples of sera were ether-extracted by the method of McFarlane.²⁹ Two volumes of serum were mixed thoroughly with one volume of ether and quickly frozen in a dry ice-alcohol bath. The sample was then allowed to thaw in the icebox for eight hours or longer, whereupon the serum layer was carefully removed from underneath the ether layer with a syringe and blunted needle. This process was repeated two additional times. McFarlane reports that this removes only part of the total lipids, but apparently does not denature the proteins.

*Species refraction increment is defined as the increase in the refractive index caused by the presence of 1 gm. of solute in 100 c.c. of solution.

†Phosphate-saline buffer mixtures of high ionic strength have been used routinely in this laboratory because (1) their boundary effects are small, (2) electrophoretically-separated samples may be assayed biologically or for nitrogen, (3) good patterns are obtainable on sera from all species so far examined, (4) all of their ions exist naturally in biological fluids, (5) when compared with the barbiturates it is relatively inexpensive.

TABLE IV. ELECTROPHORETIC FRACTIONATION OF INFANT SERA

IDENTIFICATION	COMPOSITION										METHOD OF FEEDING
	ARBITRARY UNITS					PER CENT					
	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	ALBUMIN GLOBULIN	
Umbilical Cord											
I*	520	60	70	140	790	65.8	7.6	8.9	17.7	1.9	
II	470	40	60	95	665	70.6	6.1	9.1	14.2	2.4	
IIIA†	425	40	35	110	610	69.6	6.6	5.8	18.0	2.4	
IIIB†	435	40	35	100	610	71.3	6.6	5.7	16.4	2.5	
IV	445	45	25	110	625	71.1	7.2	4.0	17.7	2.5	
V	425	40	35	95	595	71.5	6.7	5.9	15.9	2.5	
VI	555	45	40	100	730	76.0	4.8	5.5	13.7	3.2	
VII	450	30	45	160	685	65.7	4.4	6.5	23.4	1.9	
Five Days Old											
II	515	80	60	100	755	68.2	10.6	7.9	13.4	2.1	
IIIA	380	50	35	110	575	66.1	8.7	6.1	19.1	2.0	
IV	450	60	55	110	675	66.6	8.9	8.1	16.4	2.0	
V	445	50	80	110	685	65.0	7.3	11.7	16.0	1.9	
Ten Days Old											
VIII	465	55	65	110	695	67.0	7.9	9.3	15.8	2.0	Breast
IX	430	80	90	120	720	59.7	11.1	12.5	16.7	1.5	Formula
Fifteen Days Old											
VI	360	75	50	40	525	68.6	14.3	9.5	7.6	2.2	Breast
One Month Old											
VI	530	80	30	210	850	62.3	9.4	3.6	24.7	1.7	Breast
X	460	60	100	40	660	69.6	9.1	15.2	6.1	2.3	Breast
XI	555	85	70	85	795	69.8	10.7	8.8	10.7	2.3	-
Two Months Old											
VI	560	80	90	55	785	71.4	10.2	11.4	7.0	2.5	Breast
XII	450	80	80	80	690	65.2	11.6	11.6	11.6	1.9	-
XIII	400	50	40	45	535	74.8	9.3	7.5	8.4	3.0	-
Three Months Old											
VI	470	75	80	50	675	69.7	11.1	11.8	7.4	2.3	Breast
XIV	490	95	70	45	700	70.0	13.6	10.6	6.4	2.5	Formula
XV	520	75	50	35	680	76.5	11.0	7.3	5.2	3.2	Formula
XVI	575	70	100	45	790	72.8	8.8	12.7	5.7	2.7	Formula
Six Months Old											
XIV	440	75	80	30	625	70.3	12.1	12.8	4.8	2.4	Formula
XVII	655	100	110	50	915	71.6	10.9	12.0	5.5	2.5	-
XVIII	515	75	65	65	720	71.6	10.4	9.0	9.0	2.5	-
Ten Months Old											
XIX	500	45	55	60	660	75.8	6.8	8.3	9.1	3.1	-
XX	465	60	75	45	645	72.1	9.3	11.6	7.0	2.7	-
XXI	550	65	90	45	750	73.3	8.7	12.0	6.0	2.8	-

*Data for corresponding mothers recorded in Table II.

†Twins.

TABLE V. IMMUNIZATION DATA

ANTIGEN	INFANTS IMMUNIZED	
	AT BIRTH	AT 3RD, 4TH, AND 5TH MONTHS
Pertussis	XI, XII, XIII, XIV.	XIV, XVII, XVIII.
Diphtheria	XI, XII, XIII, XIV.	XIV, XVII, XVIII.
Tetanus	XI, XII, XIII, XIV.	XIV, XVII, XVIII.
Pneumococcus polysaccharide	XI, XII, XIII.	

TABLE I. ELECTROPHORETIC DATA ON PREGNANT MOTHER'S SERUM

MONTH OF PREG- NANCY	COMPOSITION									
	ARBITRARY UNITS					PER CENT				
	ALBUMIN	ALPHA- GLOBULIN	BETA- GLOBULIN	GAMMA- GLOBULIN	TOTAL	ALBUMIN	ALPHA- GLOBULIN	BETA- GLOBULIN	GAMMA- GLOBULIN	ALBUMIN GLOBULIN
2nd*	590	50	120	75	835	70.6	6.0	14.4	9.0	2.4
3rd*	515	60	100	75	750	68.7	8.0	13.3	10.0	2.2
4th*	520	80	125	75	800	65.0	10.0	15.6	9.4	1.9
5th*	500	75	145	75	795	62.8	9.5	18.2	9.5	1.7
6th*	505	90	155	85	835	60.5	10.8	18.5	10.2	1.5
7th	490	95	160	95	840	58.5	11.3	19.0	11.2	1.4
8th	460	105	170	95	830	55.3	12.7	20.6	11.4	1.3
9th	550	125	180	100	955	57.5	13.1	18.9	10.5	1.3

*From the same patient.

TABLE II. ELECTROPHORETIC FRACTIONATION OF MATERNAL SERA AT DELIVERY

IDENTI- FICATION	COMPOSITION									
	ARBITRARY UNITS					PER CENT				
	ALBUMIN	ALPHA- GLOBULIN	BETA- GLOBULIN	GAMMA- GLOBULIN	TOTAL	ALBUMIN	ALPHA- GLOBULIN	BETA- GLOBULIN	GAMMA- GLOBULIN	ALBUMIN GLOBULIN
I	420	110	170	90	790	53.1	14.0	21.5	11.4	1.1
II	430	135	150	100	815	52.8	16.5	18.4	12.3	1.1
III	360	80	180	90	710	50.6	11.3	25.4	12.7	1.0
IV	420	85	140	70	715	58.9	11.9	19.6	9.8	1.4
V	375	110	90	80	655	57.2	16.8	13.8	12.2	1.3
VI	550	85	190	90	915	60.0	9.3	20.8	9.9	1.5
VII	455	90	155	190	890	51.1	10.1	17.4	21.4	1.0

TABLE III. ELECTROPHORETIC FRACTIONATION OF FETAL SERA.

AGE IN MONTHS	COMPOSITION									
	ARBITRARY UNITS					PER CENT				
	ALBUMIN	ALPHA- GLOBULIN	BETA- GLOBULIN	GAMMA- GLOBULIN	TOTAL	ALBUMIN	ALPHA- GLOBULIN	BETA- GLOBULIN	GAMMA- GLOBULIN	ALBUMIN GLOBULIN
3	190	20	35	15	260	73.1	7.7	13.4	5.8	2.72
4	230	20	35	30	315	73.0	6.4	11.1	9.5	2.71
5	425	40	45	50	560	75.9	7.2	8.0	8.9	3.15
6	405	30	35	85	555	73.0	5.4	6.3	15.3	2.70
7	425	45	60	90	620	68.5	7.3	9.7	14.5	2.18
9	450	30	45	160	685	65.6	4.4	6.6	23.4	1.91

Almost the opposite condition prevails in the developing embryo, as is illustrated in the chart of Fig. 2 and the patterns of Fig. 4. There is a marked rise in albumin and gamma-globulin but the alpha- and beta-globulins remain at the same low throughout the period investigated (from the third month to parturition). In the first few days of postnatal life, however, alpha- and beta-globulins

increase rapidly, albumin slightly, and gamma-globulin begins to decrease. The ratio of albumin to globulin drops from 2.5 to 2.0 during the first five days, due to the rapid rise of alpha- and beta-globulins, then rises again during the next 3 weeks as a result of the marked decrease in gamma-globulin. Between the first and tenth month the albumin/globulin ratio rises again to a value of 2.7 to 3.1 as a result of the persistent low level of gamma-globulin and the substantial increase in albumin. Typical patterns of infant sera during the first year are illustrated in Fig. 5.

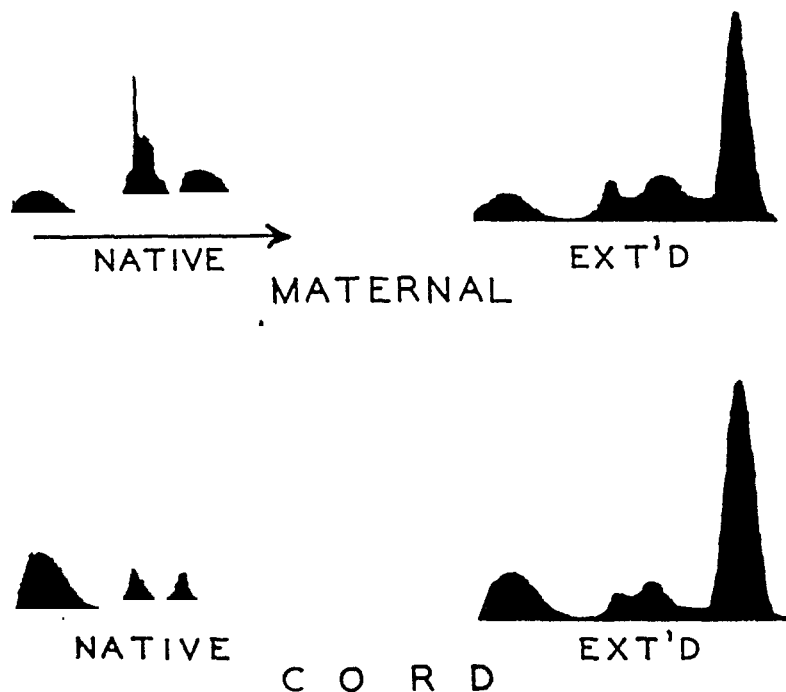


Fig. 6.—Maternal and newborn infant serum patterns before and after ether extraction.

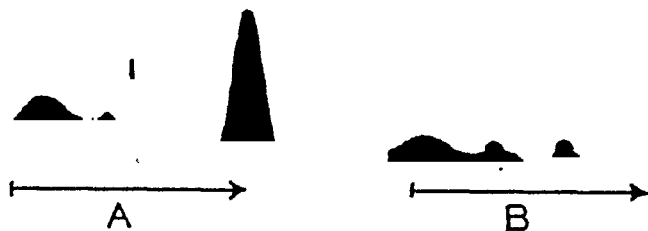


Fig. 7.—Macaque mulatto monkey serum patterns; (A) maternal at parturition, hypophysectomized 35 days prepartum, (B) newborn.

The wide fluctuations in the serum pattern of infant number VI (the daughter of one of the authors) should be noted. At birth, the pattern coincided with the average except that the albumin was slightly high. At 15 days, the total pattern area had decreased by about 30 per cent, and at one month it had more than regained its loss with an enormous increase in gamma-globulin. By the second and third months the gamma-globulin had diminished to about one-fourth the high value. No illness was noticed in the child during this period. Immunologic data are given in Table V.

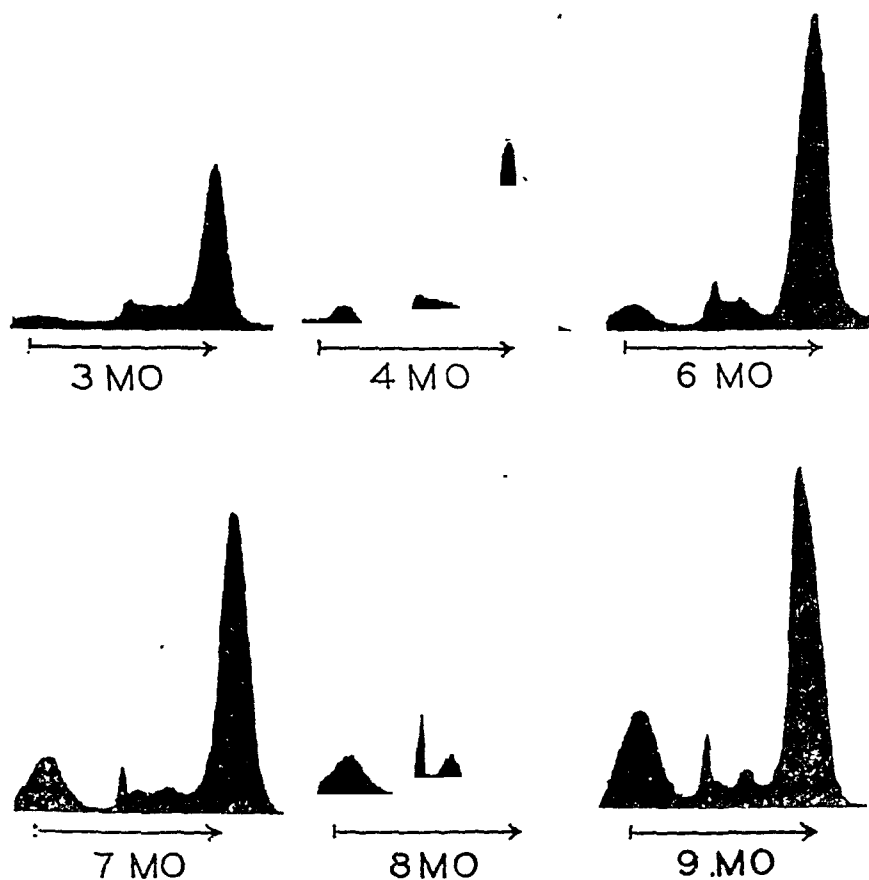


Fig. 1.—Serum patterns from developing human fetuses.

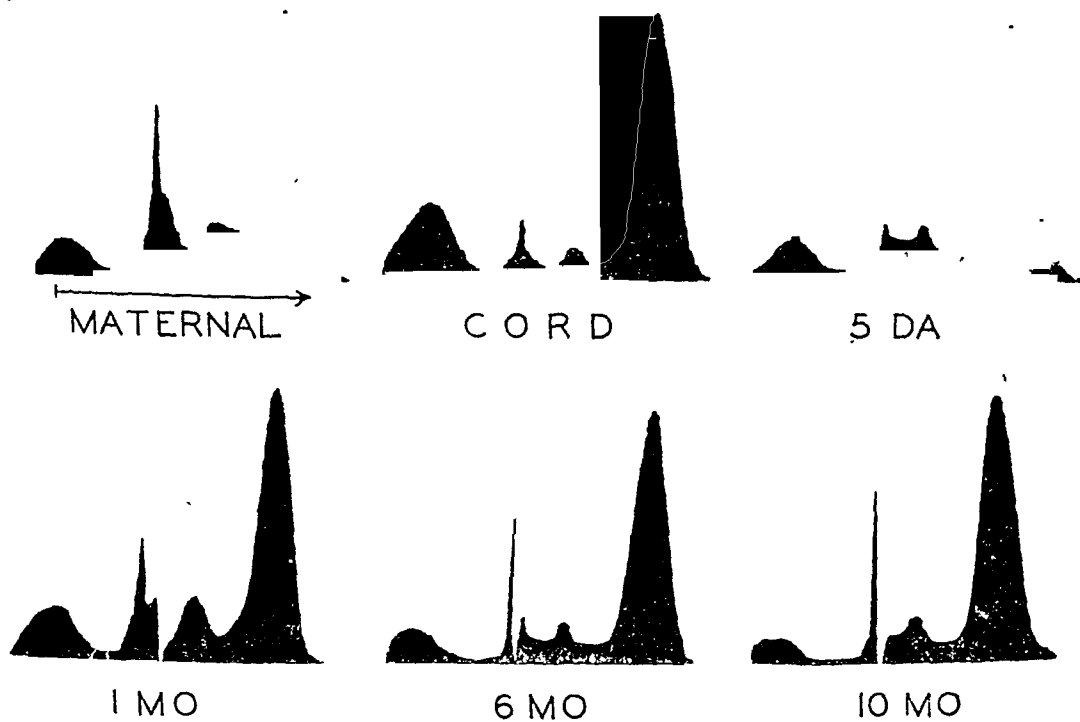


Fig. 5.—Typical maternal, newborn infant, and baby serum patterns.

extraction of the normal nonpregnant reduced essentially only the apparent beta-globulin. That this extraction procedure²⁹ removes material of low nitrogen content is evidenced by the fact that the ratio of pattern area to nitrogen was reduced upon ether extraction (see Table VI). This is in agreement with the findings of Zeldis et al.,³⁰ who extracted lipids from human and dog sera by an ether-alcohol method described by Blix.³¹ This extraction procedure is more laborious, involving precipitation of the protein. It removes more lipids than the method of McFarlane.²⁹ Such studies offer a better understanding of the changes which take place in various blood sera.

The serum gamma-globulin level during the first few months of infancy is of especial interest. Many investigators^{5, 32, 33} and others have demonstrated the presence of antibodies in newborn infant sera. Antibodies are, no doubt, a part of the gamma-globulin but in most cases³⁴ have little quantitative relation to it, as is again demonstrated here by the fact that gamma-globulin in cord sera is consistently higher than that of the maternal, whereas antibody titers are never higher.^{5, 32, 33} Moreover, there was no difference in the gamma-globulin level of sera from babies immunized with pneumococcus polysaccharide, pertussis, tetanus, and diphtheria and those unimmunized (see Tables IV and V).

If serum proteins cross from maternal to fetal blood, the placenta must play an active role in selecting the serum component transferred, since the levels of gamma-globulin and albumin are higher and those of alpha- and beta-globulin are lower in the fetal blood at birth. It has been shown by Pedersen,³⁵ however, that in human sera alpha-globulin contains the molecules having a sedimentation constant of 20 Svedberg units (molecular weight about one million), and that beta-globulin contains the large lipoprotein complexes. Neither of these large molecules would be expected to cross the placental wall as readily as the smaller albumin (mol. wt. 70,000) and gamma-globulin (mol. wt. 160,000) molecules. Nevertheless, the placenta and fetus are doubtless able to regenerate or synthesize their own blood proteins because the fetal serum pattern is little influenced by large variations found in maternal sera, particularly in toxemia¹⁴ and in the example of the hypophysectomized monkey (Fig. 6), and also because the fetus synthesizes its own proteins after birth.

Evidence for the placental transfer or placental synthesis of gamma-globulin is offered by the data of Tables II and IV (see gamma-globulin curve, Fig. 2). The decrease in gamma-globulin during the first month of postnatal life corresponds to the antibody disappearance rate one would expect from the findings of Schoenheimer et al.³⁶ They found that in the rabbit the half-life of an antibody molecule was about fourteen days. Assuming the same decay rate for the rest of gamma-globulin as for the antibodies and some postnatal replenishment, it would therefore be expected to decrease according to the curve of Fig. 2. It may be pointed out here that the flocculation of infant serum with Hayem's solution, calcium chloride, and many antigens decreases according to the gamma-globulin curve of Fig. 2.^{32, 33, 37, and others} Further evidence for placental transfer or synthesis of globulin is offered by Pommerenke,³⁸

TABLE VI. ELECTROPHORETIC DATA ON SERA BEFORE AND AFTER ETHER EXTRACTION

IDENTIFICA- TION	COMPOSITION					CHANGE					NITROGEN MG/C.C.
	ARBITRARY UNITS					PER CENT					
	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	ALBUMIN	ALPHA-GLOBULIN	BETA-GLOBULIN	GAMMA-GLOBULIN	TOTAL	
Native	420	110	170	90	790						
Maternal						-28.6	0	-58.8	0	-27.8	
Ext'd	300	110	70	90	570						
Native	530	60	70	140	790						
Cord						-24.5	0	-21.4	-7.1	-18.3	
Ext'd	400	60	55	130	645						
Native	500	90	150	90	830						2.94
Pregnancy*						-15.0	0	-46.6	-27.6	-20.5	
Ext'd	425	90	80	65	660						2.61
Native	530	90	110	110	840						
Normal						0	-22.2	-50.0	-9.1	-10.1	
Ext'd	530	70	55	100	755						
Native	740	75	170	180	1165						3.12
Lipemic†						-24.3	0	-47.0	-27.8	-26.7	
Ext'd	560	75	90	130	855						3.23

*Sixth month.

†Apparently normal male medical student.

Data obtained before and after ether extraction for pregnancy, maternal, umbilical cord, normal, and lipemic sera are reproduced in Table VI. Electrophoretic pattern areas were compared with nitrogen contents (Kjeldahl method) before and after ether extraction in two of the cases. Both electrophoretic and nitrogen analyses were made on aliquots of the same diluted and dialyzed material. Patterns of maternal and cord sera are shown in Fig. 6.

In order to demonstrate the wide divergence which may occur in the sera of mother and fetus, a comparison is made in Fig. 7 of serum from a macaque mulatto monkey hypophysectomized 35 days before delivery and from her newborn offspring.*

Discussion

The foregoing data indicate that the total electrophoretic pattern area for the newborn infant sera is smaller than that for the mothers'. The small amount of alpha- and beta-globulin in the infant sera is responsible for this difference because both the albumin and gamma-globulin areas are greater in the latter. This is in agreement with the findings of Longsworth, Curtis and Pembroke,¹² whose illustrated patterns, however, did not appear to agree (probably due to the large delta-boundary in the maternal plasma pattern) with any of their own plasma data.

The changes which occur in pregnancy serum are in agreement with the observations of Lagercrantz¹⁴ who studied many more cases than are presented here.

Ether extraction resulted in a much greater diminution in the pattern areas of the maternal and cord sera than in the normal nonpregnant serum. A large proportion of the material extractable from the maternal and cord sera had been associated with the albumin fraction as well as with the beta-globulin, whereas

*Supplied by Dr. P. E. Smith.

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who found that the venous blood of the umbilical cord contained significantly more globulin (by salt fractionation) than the arterial blood.

A rise in euglobulin after ingestion of colostrum has been reported by Lewis and Wells.³⁹ This increase was undoubtedly due to an increase in beta-globulin and perhaps also in alpha-globulin, as our results on 5- and 10-day-old infants show (see Fig. 5). Although colostrum contains antibodies,^{32, 39} its ingestion does not increase the antibody titer^{40, 41} or the quantity of gamma-globulin in man. Ratner, Jackson and Gruehl⁴² have arrived at the same conclusion from their studies on guinea pigs. On the other hand, Jameson, Alvarez-Tostado and Sorter,¹⁰ San Clemente and Huddleson,¹¹ Polson,¹² and Charlwood and Thomson⁴³ have observed that the ingestion of colostrum by newborn calves, foals and lambs caused a rapid increase in gamma-globulin which, unlike newborn infants, was almost absent at birth. Moreover, it has been shown that the gamma-globulin level remains low throughout the fetal development of pigs.¹⁵ It would appear, therefore, that the protein pattern of fetal serum depends on the type of placenta concerned and that the gamma-globulin and the antibody titer are higher at birth and decrease thereafter in human serum, whereas they are lower and increase with the ingestion of colostrum in the lower species examined.

Summary

Serum albumin and gamma-globulin increase rapidly during the development of the human fetus, whereas the alpha- and beta-globulins remain at a low level. The alpha- and beta- globulins rise appreciably and albumin decreases in maternal sera during pregnancy. The high gamma-globulin in newborn infants decreases markedly during the first month or two of life, whereas all of the other serum components rise. The view that the ingestion of colostrum maintains or raises the antibody level of infants is not supported by our findings.

The serum patterns are discussed from the viewpoint of lipid content, placental permeability, and species differences.

The authors acknowledge the valuable technical assistance of Melba Costello and Trudy Schonberger.

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really higher or lower than in Rh-positive women. In Hunt's study, 22 of 25 women who aborted habitually were found to be Rh positive. But once again, the finding, which exactly matches the expectation of 85 per cent Rh positive to 15 per cent Rh negative, has no bearing on the question whether Rh-negative women have a higher abortion rate subsequent to sensitization or not. For "habitual abortion" may very well be caused by factors other than Rh incompatibility without affecting the possibility of a raised abortion rate due to the latter. In a continuation of this study, Hunt¹¹ added 93 cases of recurrent abortion culled from approximately 75,000 women admitted to the Mayo Clinic. Among these 93, the percentage of Rh-negative women was 18.3 per cent. In 34 cases of true habitual abortion, there were seven Rh-negative women, or 20.6 per cent. These values are somewhat higher than the expected 15 per cent of Rh-negative women in the general population, but two of these Rh-negative women had Rh-negative husbands, a fact which rules out Rh incompatibility as the cause of their habitual abortion. The standard error of the first percentage of Rh-negative women is ± 4.0 per cent, and that of the second is even larger, so that no statistical significance can be attached to their differences from the expected 15 per cent.

For an adequate analysis, it would seem essential to distinguish and to determine separately the abortion rates for Rh-negative women before and after they have become sensitized. The nearest approach to this has been the separate classification of women who have had at least one infant with hemolytic disease. Race, Taylor, Cappell, and McFarlane¹² did this for 178 pregnancies of 44 women, and found 8 abortions in 108 pregnancies (7.4 per cent) prior to the delivery of an erythroblastotic infant, and three abortions in 26 pregnancies (11.5 per cent) after the delivery of an erythroblastotic infant. These are both unusually low abortion rates, as compared with those found in the large groups studied by Tietze¹³ and in the present investigation, and the small number of pregnancies in the posterythroblastotic group in particular renders that finding of no statistical significance. The study is interesting, however, as being the first to define the problem clearly. Hunt¹¹ also cites the histories of 13 patients who delivered erythroblastotic infants, but with only seven subsequent pregnancies, the occurrence of no abortions is not indicative of anything. In 122 Rh-negative women, each one of whom had at least one erythroblastotic infant, as reported by Potter,¹⁴ there were 51 abortions in 248 pregnancies (20.6 per cent) prior to the birth of an infant with the disease, and 17 abortions in 107 pregnancies (16.0 per cent) following the the birth of such an infant. (Many of these abortions were known to have been induced.) These results are suggestive; but the difference of 4.6 per cent is again without statistical significance. For all these studies, it should be pointed out that it is probably not valid to take the birth of an infant with hemolytic disease as equivalent to sensitization. In the Baltimore Rh Typing Laboratory, erythroblastosis has occurred in the offspring of only 53, or 67.0 per cent, of 79 isoimmunized women¹⁵; and a milder, incipient degree of immunization, too weak to produce clinical symptoms of erythroblastosis, might conceivably produce early miscarriage.

The latest study on this subject, by Overstreet, Traut, Hunt, and Lucia,¹⁶ although it is considerably more extensive than any of those previously discussed, has again estimated the abortion rate for all Rh-negative women, irrespective of their immunization. The use of the first five lunar months, instead of the first seven, to define the period of miscarriage and abortion, renders these data rather less comparable with those of other studies, including the present one. One thousand thirty-eight pregnancies of 226 Rh-negative women were compared with 1,129 pregnancies of 237 Rh-positive women. No exclusion was made of Rh-negative women who had Rh-negative husbands, nor was there any

THE RELATION OF RH INCOMPATIBILITY TO ABORTION

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IN 1928, Hirszfeld¹ observed that there seemed to be a higher than random occurrence of incompatible ABO matings among women with histories of two or more abortions. Influenced by that observation, Levine,^{2, 3} early in the course of his studies on the relation of the Rh blood factors to erythroblastosis fetalis, suggested that perhaps Rh incompatibility between mother and fetus might give rise to abortions and miscarriages, as well as to stillbirths. In a later paper,⁴ he recorded the high rate of ten abortions or miscarriages in 37 pregnancies of seven patients. It is not clear, however, from the report, whether this rate of 27 per cent abortion was in a group made up wholly of Rh-negative women or not; nor was the distribution of abortions among the mothers given. Later in 1943, Schwartz and Levine⁵ examined nine cases of mothers who had had two or more early abortions in succession. Eight of these nine women turned out to be Rh positive, and these workers then concluded, on this rather slight basis, that while Rh incompatibility may well produce late abortions, i.e., in the second trimester of pregnancy, it is quite unimportant in bringing about early abortions. Yet against any such positive conclusion as to the role of Rh incompatibility even in late abortion were their own data, which showed that of 11 premature births, only one involved an Rh-negative mother.

Beside these observations and conjectures one must place the findings of Bornstein and Israel⁶ of definite Rh antigen in a 17 cm., 4-month-old un-macerated fetus, and the finding by Kemp⁷ of B antigen in a 37-day-old fetus. Although so early a development of antigens would render early maternal iso-immunization at least possible, it was reported, on the other hand, by Page, Hunt, and Lucia⁸ that ten weeks of antibody production are required to produce appreciable fetal damage. The sum of four months and ten weeks would render dubious any likelihood of Rh incompatibility leading to abortion prior to the twenty-eighth week of pregnancy, the term customarily chosen for delimiting miscarriage and abortion, on the one hand, from premature birth on the other.

The question raised was not greatly clarified by the further data reported by Potter, Davidsohn, and Crunden,⁹ and by Hunt.¹⁰ These investigations merely ascertained the frequency of Rh-negative women among women who aborted under observation or were known to have histories of habitual abortion. In the first of these two studies, 40 of 45 women who aborted were Rh positive, 5 of 45 were Rh negative. But this finding that abortions may occur in Rh-positive women as well as Rh-negative women is hardly surprising; and the 11 per cent frequency of the Rh-negative women in this group, where about 15 per cent is to be expected, has a standard error of ± 4.7 per cent. No conclusion is possible, therefore, as to whether the abortion rate in Rh-negative women is

TABLE I. ABORTIONS PER PREGNANCY IN THE TOTAL WHITE POPULATION STUDIED

GRAVIDA	ORDINARY PREGNANCY										TOTAL	PER CENT
	1ST	2ND	3RD	4TH	5TH	6TH	7TH	8TH	9TH	10TH PLUS		
i	197/1684										197/1684	11.70 ± 0.78
ii	118/831	157/831									275/1662	16.55 ± 0.91
iii	58/362	64/362	84/362								206/1086	18.97 ± 1.19
iv	16/118	20/118	20/118	20/118							76/472	16.10 ± 1.7
v	12/79	13/79	11/79	9/79	18/79						63/395	15.95 ± 1.8
vi	3/37	4/37	5/37	6/37	9/37	6/37					33/222	14.86 ± 2.4
vii	7/34	3/34	6/34	5/34	7/34	2/34	5/34				35/238	14.71 ± 2.3
viii	1/11	0/11	4/11	1/11	3/11	5/11	2/11	3/11			19/88	21.59 ± 4.4
ix	0/6	0/6	0/6	0/6	0/6	0/6	1/6	0/6	0/6		1/54	18.52 ± 5.3
x	1/9	1/9	0/9	1/9	1/9	2/9	1/9	5/9	2/9	8/21	22/102	21.57 ± 4.1
Total	413/3171	262/1187	130/656	42/294	38/176	15/97	9/60	8/26	2/15	8/21	927/6003	
Per cent	13.02 ± .60	17.62 ± .99	19.82 ± 1.56	14.20 ± 2.0	21.6 ± 3.1	15.5 ± 3.7	15.0 ± 4.6	30.8 ± 9.1	13.3 ± 8.8	38.1 ± 10.6		15.44 ± 0.47

Diagonal line separates: Prior half histories: 14.7 ± 0.76 per cent Latter half histories: 19.1 ± 0.85 per cent

separation of Rh-negative sensitized from nonsensitized women. The total abortion rate found was 15.2 per cent for Rh positive, 12.4 per cent for Rh negative, the difference being attributed to sampling error. A definite rise in abortion in multigravidas, as compared with primigravidas, was found in both groups: Rh positive, from 12.2 per cent to 17.8 per cent; Rh negative, from 10.9 per cent to 13.9 per cent. It was not recognized, however, that the higher average number of pregnancies in the Rh-positive group would quite account for the difference between the Rh-positive and Rh-negative groups in the abortion rate.

Forty-five mothers who had borne an erythroblastotic child were given separate consideration. The abortion rate for all pregnancies of these women was 14.1 per cent, with a rise from 6.7 per cent in the first pregnancy to 17.8 per cent in multigravid pregnancies. The differences between these values and those for the Rh-positive control group are, however, not significant. The authors, while not claiming to have disproved that a relation between Rh incompatibility and abortion may exist, yet concluded that, since the Rh antigen probably does not develop in the first two to four weeks of pregnancy, and since about ten weeks thereafter are required for sensitization to reach a level sufficient to do appreciable fetal damage, there can be little chance of this occurring before twenty weeks, the onset of the viable period.

Hunt¹⁴ has added a study of 228 Rh-positive and 228 Rh-negative women, with 36 abortions and miscarriages in 377 pregnancies (9.5 per cent) in the former, and 48 in 333 (14.4 per cent) in the latter. The difference is not statistically significant, and is in the opposite direction to that found in the larger group studied by Overstreet and associates.¹⁵

One may summarize all the studies reviewed above by saying that in a statistical sense they have failed either to establish or to disprove the existence of a relation between Rh isoimmunization and abortion. A final answer to this question can be given only by comparing an adequate sample of the histories of Rh-negative women, dating from the onset of sensitization in each case, with those of a carefully matched control group.

Present Study

In previous discussions of the possible relation of Rh incompatibility to miscarriage and abortion, the question does not appear ever to have been clearly posed. For statistical assurance, it is necessary to put it in the following terms: Is there any significant difference between the frequency of abortion and miscarriage in Rh-negative women, known to be actually sensitized, and for those particular pregnancies in which the fetus is Rh positive, and the frequency of abortion and miscarriage in other women?

When the problem is framed in these terms, it becomes clear that studies of the total frequency of abortion and miscarriage in all Rh-negative women, as compared with Rh-positive women, serve to obscure rather than to clarify the issue. In the first place, fetuses that are Rh negative themselves, in an Rh-negative mother, would not be expected to abort by reason of Rh incompatibility, irrespective of whether or not the mother is sensitized. Such cases represent 27.7 per cent of the pregnancies of Rh-negative women married to Rh-positive men (Rh-positive heterozygotes = 55.4 per cent of all Rh-positive individuals, and one-half of the children of such unions would be Rh negative). Since about 28 per cent of the pregnancies of Rh-negative sensitized women are therefore not

TABLE II. INCIDENCE OF ABORTION IN TWO INDEPENDENT SAMPLES OF 1,250 RH-POSITIVE WOMEN (MATCHED FOR GRAVIDITY i, ii, iii, AND iv OR MORE)

	ORDINAL PREGNANCY					
	1ST	2ND	3RD	4TH	5TH	6TH 7TH PLUS
	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.
Sample 1	158/1250	161/919	110/589	43/292	28/159	32/133
Sample 2	158/1250	154/919	119/589	51/292	29/146	14/78
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Sample 1	12.63	17.5	18.7	14.7	17.6	24.02
Sample 2	12.63	16.76	20.2	17.46	19.85	17.95

TABLE III. FREQUENCY OF ABORTION IN RH-POSITIVE, RH-NEGATIVE NONSENSITIZED, AND RH-NEGATIVE SENSITIZED WOMEN

	ORDINAL PREGNANCY					
	1ST	2ND	3RD	4TH	5TH	6TH 7TH PLUS
	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.	ABORT./PREG.
Rh-	291/2500	193/1252	101/626	37/323	33/212	16/112
Rh- nonsens.	134/1155	86/546	41/260	19/133	12/80	2/39
Rh- sens.	25/209	18/142	17/89	7/52	11/35	3/22
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Rh-	11.64 ± 0.64	15.42 ± 1.02	15.97 ± 1.46	11.5 ± 1.8	15.6 ± 2.5	14.3 ± 3.3
Rh- nonsens.	11.6 ± 0.94	15.7 ± 1.56	15.75 ± 2.26	14.3 ± 1.9	15.0 ± 4.0	6.9 ± 4.1
Rh- sens.	11.95 ± 2.24	12.68 ± 2.8	19.1 ± 4.2	13.44 ± 4.3	31.4 ± 7.85	13.6 ± 7.4

pertinent to the point at issue, a considerable number of such pregnancies must be studied to render any but a large differential statistically significant. In other words, unless very large numbers of cases are studied, the absence of any apparent difference in abortion frequency between Rh-negative sensitized women and their controls is likely to be due to the inclusion of Rh-negative offspring among the offspring of the Rh-negative sensitized women, rather than to the absence of any real difference. On the other hand, any differential that can be found and established statistically is really far larger than would appear at first sight, unless this bias has been allowed for.

Division of the individual subjects into three groups, the Rh positive, the Rh negative nonsensitized, and the Rh negative sensitized, is no less important to a clear analysis. The first two classes can be readily and accurately determined on the basis of tests during the current pregnancy, but without a complete history of tests made during each past pregnancy from the first on, the classification of the third group entails an unavoidable bias. Only for women in their first pregnancy, or for a certain few in their second, could it be positively determined, in the present study, at which pregnancy the sensitized condition had arisen. Consequently, in classifying women as sensitized solely on a current basis, an undeterminable number of pregnancies were classed as sensitized when they ought really to have been classed as nonsensitized. The two-year survey of the Baltimore Rh Laboratory reports the initial occurrence of isoimmunization in 228 multigravidas as 45.6 per cent in the second pregnancy, 21.5 per cent in the third, 13.6 per cent in the fourth, 4.8 per cent in the fifth, 8.3 per cent in the sixth, etc. Thus 54.4 per cent of the women eventually sensitized were not yet sensitized in their second pregnancy, 32.9 per cent in their third, and 19.3 per cent in their fourth. It can therefore be estimated that nearly all first pregnancies of women eventually sensitized were nonsensitized, as well as about one-half of the second pregnancies, about one-third of the third pregnancies, and about one-fifth of the fourth pregnancies. Consequently, any observed difference in the frequency of spontaneous abortion between women classified into "sensitized" and "nonsensitized" on the basis of their condition in current pregnancies should be increased by corresponding fractions. This consideration makes it clear that if a real difference in frequency of abortion should exist, it would, in a study such as the present, where the actual incidence of the sensitized state is not known for most of the subjects, be necessary to tabulate the frequencies of abortions by ordinal pregnancies. No difference can be expected to emerge until at least the third pregnancy is reached.

The frequencies of abortion are known¹³ also to increase with increasing family size, at least in certain social and economic categories of the population. It was accordingly decided to tabulate the abortions also according to the gravidity of the women. The result of the dual tabulation was a triangular table, such as that presented for the total white population in Table I. This table reveals an abortion frequency of 15.44 per cent in the 6,003 pregnancies of the 3,171 white women included in the study.

The data used in the investigation consisted of the obstetric histories taken by regular workers at the Baltimore Rh Laboratory. Each woman was asked to give the date and outcome of every one of her pregnancies. Termination of any pregnancy prior to the twenty-eighth week from the last menstruation was regarded as an abortion (or miscarriage). Only in a few instances was information given as to whether the abortion was spontaneous or not. All abortions, including those induced, were therefore included in the data, inasmuch as no reliable criteria for separating spontaneous from induced abortions appeared to exist. Although this fact may be taken to mean that the "real" frequencies

Rh-negative sensitized women actually have a slightly higher abortion frequency than Rh-positive women; but this is due to nothing more than their higher average order of pregnancies. This is in harmony with the already known fact that abortion frequency tends to increase with increasing gravidity.

Table III and Fig. 1 present the comparison of abortion frequency, by ordinal pregnancies, for the three groups of women. It should be kept in mind that as the number of pregnancies progressively drops in the higher classes, the statistical error consequently increases in inverse ratio. This is especially true of the Rh-negative sensitized group, a small sample to start with. For example, whereas the standard error of the rate for the first pregnancy of the Rh-positive group is only ± 0.64 per cent, for the sixth pregnancy of the Rh-negative sensitized group it is ± 7.4 per cent.

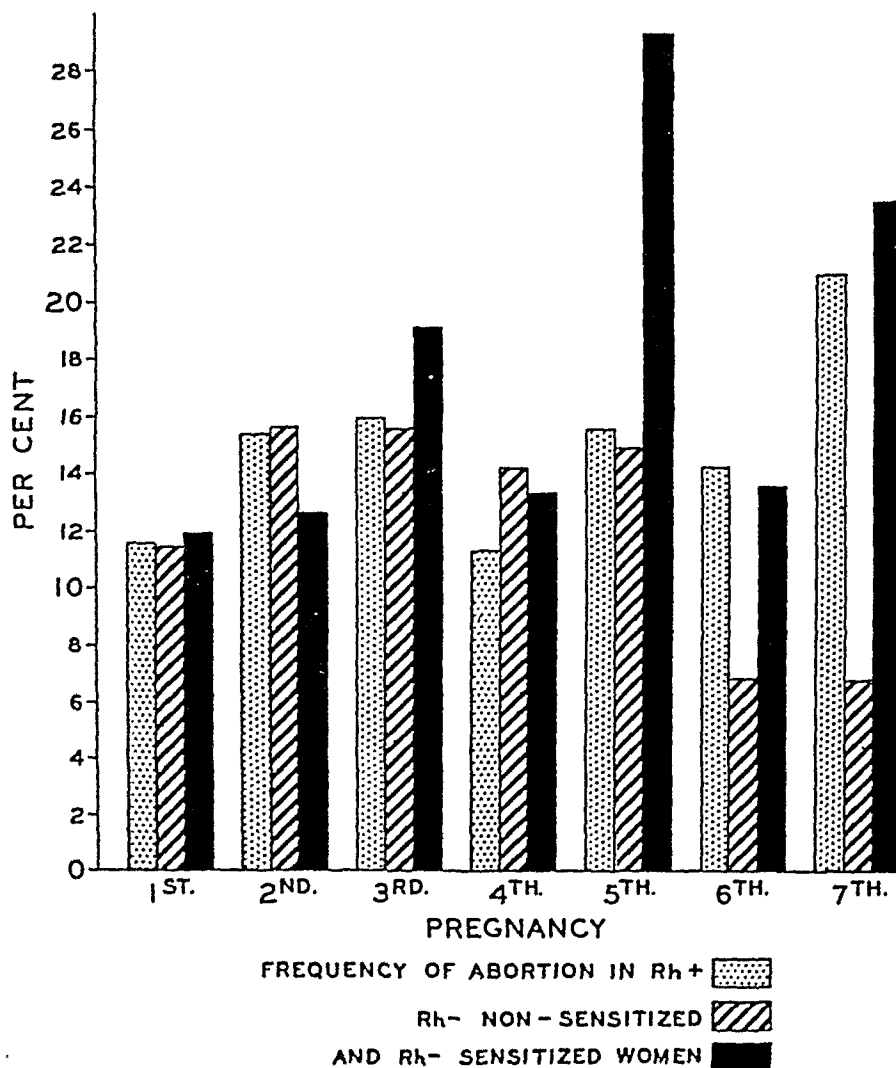


FIG. 1.—Frequencies of abortion in Rh-positive, Rh-negative nonsensitized, and Rh-negative sensitized women, by ordinal pregnancies.

For reasons previously pointed out, it would seem that all Rh-negative women might be considered together for their first through third pregnancies, for comparison with the Rh-positive group. The percentage of abortion for the combined first to third pregnancies, inclusive, for Rh positive and total Rh negative actually turns out to be identical (13.37 per cent).

of spontaneous abortion are quite different from those reported, such a conclusion by no means invalidates the study. The subjects' histories were taken prior to their being typed for Rh. Untruthfulness and forgetfulness, as well as ignorance regarding very early miscarriage, may be assumed to have operated equally in the three groups of Rh-positive, Rh-negative sensitized, and Rh-negative nonsensitized women. The statistical reliability of the information was further checked by drawing two independent samples, of 1,250 women each, matched for gravidity, from the Rh-positive group. This comparison is set forth in Table II. None of the differences between corresponding classes of the two samples in Table II is statistically significant. In fact, in only one case, that of the 7 plus class, does the difference so much as equal twice the standard error of the mean of the two samples. In most cases the difference is less than the standard error.

The frequency of the Rh-negative type in Negroes is well known to be considerably below that in whites (slightly over one-half, in American Negroes). Therefore, in order to make the Rh-positive and Rh-negative groups comparable, it was necessary to match the proportion of Negroes in the Rh-positive samples against that in the two-Rh-negative groups. The frequency of Negroes in both Rh-negative groups (sensitized and nonsensitized combined) was taken as a basis for the quota of Negroes to be included in the Rh-positive group, and Negro individuals of equal gravidity were selected at random from the files to match those in the (combined) Rh-negative group. The number of women of other nonwhite ethnic groups was so small that they were all excluded from the study.

One other precaution was taken in order to make the three groups comparable. Each Rh-negative woman is followed up in the laboratory throughout the course of her current pregnancy and through delivery. This is not true of the Rh-positive women. It was early discovered that certain factors reduce the frequency of abortions reported for current pregnancies, in general. It was therefore necessary to exclude all data from the current pregnancy of each woman, and to rely upon records of past pregnancies alone. This unfortunately reduced the total number of pregnancies for the two Rh-negative groups, and so diminished the statistical information derivable from the full data; but it seemed necessary in order to make the three groups strictly comparable.

Comparison of the Three Groups

The ratio of total reported abortions and miscarriages to pregnancies was 701/5,168, or 13.56 per cent, for the 2,500 Rh-positive women; 297/2,247, or 13.2 per cent for the 1,155 Rh-negative nonsensitized women; and 89/583, or 15.25 per cent, for the 209 sensitized women. The total Rh-negative group, with 386/2,830 abortions, or 13.62 per cent, is obviously not different from the Rh-positive group. The difference between the Rh-positive and the Rh-negative sensitized women is also without significance ($\chi^2 = 1.3$; $P = 0.30-0.20$). It should be noted that the Rh-negative nonsensitized group has a smaller average number of pregnancies per woman (1.945), and the Rh-negative sensitized group a higher one (2.790), than the Rh-positive group (2.067). This must be due to an increasing probability that a Rh-negative woman will become sensitized as she has additional pregnancies, a factor that brings about a regular shift of individuals from the Rh-negative nonsensitized group to the sensitized group;* for when the two Rh-negative groups are combined, the average number of pregnancies (2.001) is very close to that of the Rh-positive group, as is to be expected, since the latter was indeed selected to correspond to the total Rh-negative group in gravidity frequencies. One may conclude, therefore, that

*That is to say, for example, the data for the fifth pregnancy are more largely contributed by v-gravida women for the Rh-negative nonsensitized group, but predominantly by women of higher gravidity for the Rh-negative sensitized group.

the pregnancy history than in the prior half. This is apparent from an inspection of Table I, where the rate for the prior half of the histories is 14.7 per cent, and for the latter half 19.1 per cent. In Table VB, the actual values of abortion frequency in the Rh-positive women are compared with the values expected if abortion is equally frequent in prior and latter portions of pregnancy histories. The χ^2 values are particularly large for the ii-gravida, vi-gravida, and ix plus-gravida classes, being significant for each of these at the 1 per cent level. Since the difference holds true for each class, regardless of whether the gravidity is low or high, it may be assumed to mean that women have either an inherent or a psychologically conceived individual pattern of family size (i.e., number of pregnancies), and that as this is approached and exceeded, biological factors or voluntary actions tend more and more strongly to increase abortion. This is not a very startling conclusion, but it would appear to be the first time any quantitative evidence has been forthcoming to support it.

In the Rh-negative groups, no such relation is apparent. This is probably merely due to the statistical unreliability of small samples, inasmuch as the larger deviations, at least in the ii-gravida and iv-gravida classes of the non-sensitized group favor the latter half of the pregnancy history.

Summary

1. A total frequency of abortion of 15.44 per cent was reported in the 6,003 pregnancies of the 3,171 white women studied.

2. No significant increase in abortion was found in the histories of 209 Rh-negative sensitized women. A slight rise, if real, may be accounted for by the higher average number of pregnancies per woman in this class, in comparison with the Rh-positive and especially with the Rh-negative nonsensitized groups.

3. The analysis of 2,500 histories of Rh-positive women discloses a highly significant increase in abortion in the latter half history, irrespective of gravidity.

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A test for the significance of differences in the abortion rates for the several ordinal pregnancies may be made in spite of the complicating factor of the known increase in abortion frequency with advancing gravidity. This is performed by calculating the expectancy for women of each gravidity separately, on the general assumption that the incidence of abortions for women of any one gravidity is equally distributed among their pregnancies (1st to n th).

TABLE IV. TESTS OF SIGNIFICANCE OF DIFFERENCES IN ABORTION FREQUENCY AT DIFFERENT ORDINAL PREGNANCIES

	ORDINAL PREGNANCY							
	1ST	2ND	3RD	4TH	5TH	6TH	7TH PLUS	TOTAL
<i>Rh+</i>								
Expected	323.5	191.5	90	40	22	12	21	700
Obtained	291	193	100	37	33	16	30	700
Dev.	-32.5	+1.5	+10	-3	+11	+4	+9	
$\chi^2 = 15.34$; for 6 degrees of freedom, $P = 0.02 - 0.01$								
<i>Rh- nonsensitized</i>								
Expected	148	76	37	17	11		8	297
Obtained	134	86	41	19	12		5	297
Dev.	-14	+10	+4	+2	+1		-3	
$\chi^2 = 4.51$; $n' = 5$; $P = 0.50 - 0.30$								
<i>Rh- sensitized</i>								
Expected	25	21	14	9	7.5	5	7.5	89
Obtained	25	18	17	7	11	3	8	89
Dev.	0	-3	+3	-2	+3.5	-2	+0.5	
$\chi^2 = 3.97$; $n' = 6$; $P = .70 - .50$								

TABLE V. TESTS OF SIGNIFICANCE OF DIFFERENCES IN ABORTION FREQUENCY IN EARLIER VS. LATER PORTIONS OF PREGNANCY HISTORIES

<i>A. Ordinal pregnancy</i>									
	1st + 2nd			3rd + all subsequent					
Expected	515			185					
Obtained	484			216					
Dev.	-31			+31					
$\chi^2 = 7.06$; $n' = 1$; $P < 0.01$									
<i>B. Gravidity classes</i>									
	2	3	4	5	6	7	8	9+	
Expected	101.5	76	34.5	25.5	10.5	14	7.5	14.5	
Obtained (prior half history:	84:119	67:85	33:36	20:31	4:17	11:17	5:10	5.5:23.5	
latter half history)									
Dev.	+17.5	+9	+1.5	+5.5	+6.5	+3	+2.5	+9	
$\chi^2 =$	6.12	2.12	0.12	2.38	8.04	1.28	1.66	11.18	Total 32.9
$n' = 8. \quad P < 0.001$									

The results of this analysis are shown in Table IV. They clearly indicate that only in the Rh-positive group is there any real departure from expectation. For this group, the deviations from expectation are located chiefly in alternate pregnancies, the first, third, fifth, and seventh plus. The meaning of this becomes clearer if a different grouping of the data is adopted, as in Table V. First, the hypothesis that the early pregnancies (first and second) for women of all gravidity classes have a lower rate of abortion than later pregnancies (third and higher) is tested, and shown to be correct (Table VA). Then the slightly different hypothesis that the earlier half of the pregnancies of the women in each gravidity class (excluding primigravidas) has a lower abortion rate than the second half is likewise tested, and found to be quite beyond doubt. For every class, there is clearly a higher abortion frequency in the latter half of

TABLE II. DISTRIBUTION BY GRAVIDITY

GRAVIDA	I	II	III	IV	V	VI	VII	VIII	XI	XII	XVII
No. of cases	261	138	82	28	10	4	3	5	1	1	1

All patients were at least four and one-half months pregnant, as shown in Table III.

TABLE III. TERM OF GESTATION

MONTHS	4½-5	5-6	6-7	7-8	8-9	9	9 PLUS
No. of cases	1	2	2	10	48	453	18

The pelvis was considered to be normal or gynecoid in 428 of the patients. The other types and corresponding fetal mortality, including that from intracranial hemorrhage, are shown in Table IV.

TABLE IV. "CLINICAL" CLASSIFICATION OF PELVIS

	NO. OF PATIENTS	MATERNAL DEATHS	FETAL DEATHS	INTRACRANIAL HEMORRHAGE
Gynecoid	428	1	23	7
Small gynecoid	23		2	0
Platypelloid	46		4	3
Anthropoid	14		0	0
Android	23		2	2

There are not enough cases of intracranial hemorrhage associated with the three abnormal types of pelvis to draw definite conclusions, but the trend is in accordance with the generally accepted concept that the android pelvis is the most dangerous type for the performance of internal podalic version and extraction.

Indications

TABLE V. INDICATIONS FOR VERSION

INDICATIONS	NUMBER	MATERNAL DEATHS		FETAL DEATHS	
		NUMBER	PER CENT	NUMBER	PER CENT
Inertia	220	1	0.45	12	5.4
Persistent posterior	59			0	
Transverse arrest	50			3	6.1
Failure of descent	24			1	4.1
Prophylactic	92			3	3.2
Relative disproportion	26			0	
Fetal distress or prolapsed cord	24			4	16.6
Transverse presentation	13			1	7.6
Face presentation	5			0	
Premature separation placenta	7			3	42.8
Placenta previa	3			1	33.3
Toxemia	3			1	33.3
Abnormalities of cervix	5			0	
Hydrocephalic	2			2	100.
Prolapsed hand	1			0	

There were fifteen indications given for performing version. The group composed of inertial labor, failure of descent, transverse arrest, and persistent posterior was by far the largest, accounting for 353 of the 534 cases. Frequently two of these were listed as indications, since they are usually complementary, but we have selected the one listed first on the chart for purposes of classification. Ninety-two versions, including twenty-six on a second twin were done "prophylactically." Most of these were multiparas, completely dilated, having poor

INTERNAL PODALIC VERSION AND EXTRACTION

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INTERNAL podalic version and extraction is an obstetric procedure hallowed by time. However, proponents of routine versions have appeared at intervals to cause consternation and controversy in the medical profession, so that at the present time the value of this procedure is frequently overlooked. While it is true that a breech presentation is a major obstetric complication, the extraction following an internal podalic version is not the same for the three inherent dangers of breech extraction, namely extended arms, an extended head, and an un moulded head, are usually avoided. When a high fetal or maternal mortality rate follows version and extraction, it generally means that the prerequisites and contraindications have not been observed, or the operator has had too little experience with the procedure. Extended or nuchal arms are almost always to be blamed on the operator. A timely version eases the accoucheur out of many a difficult situation. Especially is this true in the handling of inertial labors.

Material Studied

In the three and one-half years from Jan. 1, 1944, to July 1, 1947, 534 babies of 12,895 labors were delivered at the Elizabeth Steel Magee Hospital by internal podalic version and extraction. Twenty-eight of these were one of twins. This is a frequency of 4.1 per cent, or one version of every twenty-four deliveries. In comparison, Delfs and Eastman³ report 0.9 per cent and Assali and Zacharias¹ 0.79 per cent. With this number of cases we feel qualified to speak on the merits and demerits of this procedure, for we have not the biased viewpoint of either the routine versionist or the inherent disbeliever in the operation.

Of the 534 patients, 495 were private and thirty-nine ward, including seventeen Negro patients. Of these, 436 deliveries were performed by obstetricians, including thirty-nine in consultation, twenty by men predominantly gynecologists, thirty-nine by residents, and thirty-nine by visiting staff members qualified to do operative obstetrics.

Age, Parity, and Term of Gestation

The ages of the patients varied between sixteen and forty-three, 245 patients being 30 years old or over. There were twenty-three primigravidas 35 years of age or older. Two hundred sixty-one patients were primigravidas and 273 multi-gravidas. The latter ranged from gravida ii to gravida xvii.

TABLE I. AGE DISTRIBUTION

AGE GROUPS	16-19	20-29	30-39	40-43
No. of cases	10	279	229	16

means probably that the physiologic retraction ring was present in greater degree than usual, but obviously there could have been no true pathologic ring, or there would have been more ruptured uteri. There was only one ruptured uterus in this series, which is far below the number reported by Delfs and Eastman³ or Cosgrove and associates² of 1:80 or 1:77 versions, respectively. Our patient was a 20-year-old unmarried Negro woman, gravida i, who started in labor at term. The pelvis was anthropoid, the length of labor forty-eight hours, and the membranes were intact with complete dilatation of the cervix. Due to inertia and a persistent posterior, the resident physician attempted delivery by version, but found a Bandl's ring prevented him from displacing the head. A staff man then attempted delivery, but in the effort ruptured the lower uterine segment transversely. The patient was taken to the operating room, and by lengthening the rupture a low cervical section was carried out. Plasma and penicillin were used, and mother and baby were discharged from the hospital in good condition after an afebrile postoperative course.

A previous section in two patients and a previous myomectomy in one were added risks of delivery.

TABLE VIII. COMPLICATIONS OF DELIVERY

Nuchal arm	3
Bandl's ring	26
2° laceration of perineum	169
3° laceration of perineum	7
Cervical laceration	30
Sulcus laceration	49
Manual removal of placenta	69
Packing of uterus	46
Plasma transfusions	18
Blood transfusions	1
Voorhees bag	3
Dührssen's incisions	1
Manual dilatation of cervix	10
Ruptured uterus	1

Piper forceps to the aftercoming head were employed in only twenty-nine instances, usually when manual flexion of the head proved difficult. We feel the use of forceps to the aftercoming head should be employed more often than in this series, so that flexion and extraction of the head can be carried out with less danger or damage to the fetus.

Postpartum Complications

There was one maternal death in the series. This patient, a 26-year-old, gravida i, was admitted to the hospital in inertial labor one week after her estimated date of confinement. After nine hours of labor the membranes were ruptured artificially, but the labor pains continued inertial in type. Thirty-six hours after the onset of labor she was completely dilated, and the baby was in a left occipitoposterior position. A fairly difficult version and extraction was performed, with delivery of a 7 pound 12 ounce infant. The patient was never fully aroused from the anesthetic, being markedly cyanotic. A medical consultant found moist râles and bronchial breathing in both lung bases, and diagnosed the condition as pulmonary atelectasis. The uterus remained firm, and there was no evidence of hemorrhage. Three and one-half hours after delivery the patient had a complete circulatory collapse and died. Permission for an autopsy could not be obtained. The infant died eighteen hours after delivery from a probable intracranial hemorrhage.

The other postpartum complications are listed in Table IX. A dilatation and evacuation was performed on the eleven patients with retained placental tissue as advocated in a previous paper.⁵

pains, and with the head high in the pelvis. Relative cephalopelvic disproportion accounting for twenty-six versions, fetal distress and/or prolapsed cord accounting for twenty-four versions, and transverse and face presentations accounting for eighteen versions were the remaining sizable categories. All other indications accounted for but a few cases each.

Not listed among the indications per se is a group of twenty-six attempted forceps. Many of these were consultation cases where attempted forceps had resulted in the head being pushed out of the pelvis or to a posterior position, and some were cases in which forceps extraction was considered to necessitate too much force for the welfare of the baby, and version was substituted as the safer method of delivery. Forty-two patients had been delivered by version previously, and one had had three previous versions.

Duration of Labor

The duration of labor is shown in Table VI. In 205 of the deliveries labor extended over eighteen hours, generally stated as the average duration of labor in the primigravida. The longest labor was one hundred and fifty hours. This confirms Rudolph's¹⁰ contention that the "time element in a labor is of little value in determining the loss of uterine tone" and, accordingly, the danger of rupture of the uterus from doing a version.

TABLE VI. DURATION OF LABOR

HOURS	ALL CASES	PRIMIPARAS	MULTIPARAS
Up to 12	219	55	164
13 to 18	104	50	54
19 to 40	159	114	45
41 to 60	34	27	7
61 to 80	6	2	4
81 to 100	4	4	0
100 plus	2	1	1
Unknown	6	1	5

Ruptured Membranes

The membranes were definitely known to be ruptured prior to delivery in 254 cases. They were ruptured at delivery in 260 instances, and the status is unknown in twenty cases. The length of time ruptured membranes existed prior to delivery varied from one-half hour to five days.

TABLE VII. RUPTURED MEMBRANES

HOURS	NO. OF CASES	HOURS	NO. OF CASES
1/2 to 2	57	36 to 50	21
3 to 5	35	51 to 75	12
6 to 10	41	76 to 100	5
11 to 20	48	100 plus	3
21 to 35	32	Unknown	20

We do not feel that ruptured membranes are a contraindication to version. As long as the head can be easily displaced and the tonus of the uterine musculature is such that it will stretch adequately for internal manipulation a version can be performed without danger of rupture.

Complications of Delivery

Table VIII shows the complications encountered at the time of delivery. Many of the cervical lacerations would have passed unnoticed, except for the fact that we examine all cervixes in primigravidas and many in multiparas immediately following a version. The mention of Bandl's ring as a complication

2 ounces. Of the twelve patients delivering children dying from intracranial hemorrhage, nine were delivered by obstetricians (four in consultation), two by gynecologists, and one by the resident staff.

Besides the fatal injuries there were six infants with fractured clavicles, three with fractured humeri, four with brachial paralysis, and one with an intracranial hemorrhage. As far as known, none of these resulted in permanent injury or damage.

Discussion

Excluding the ninety-two "prophylactic" versions and extractions, the gross fetal mortality rate in this series was 6.3 per cent, and corrected 3.8 per cent. It must be remembered that each of these cases was a primarily difficult obstetric problem. The handling of inertia, persistent posterior, relative cephalopelvic disproportion, failure of descent, etc., is not easy. Only recently Schmitz and associates¹¹ reported a study of 224 cases of prolonged labor treated ultraconservatively (only three versions were performed) with a gross fetal mortality of 7.4 per cent (corrected 6.69 per cent). Statistics on high and midforceps are listed in Table XII.

TABLE XII

	HIGH FORCEPS DEATHS			MIDFORCEPS DEATHS		
	CASES	% FETAL	% MATERNAL	CASES	% FETAL	% MATERNAL
Kjelland ⁶		4.54	0.91			
von Schubert ¹²	50	6.	4.			
Martin ⁷	67	30.5	7.5	193	8.7	0.5
Miller ⁸	19	10.5		200	5.	
Assali	222	17.8	?	852	4.6	?

Available reports on version and extraction in recent years perhaps justify the apparent fear in which the operation is held.

	CASES	MATERNAL DEATHS		FETAL DEATHS	
		NUMBER	PER CENT	NUMBER	PER CENT
1940 Cosgrove ²	221	2	0.9		30.8
1940 Miller ⁸	76	0		25	32.8
1940 Martin ⁷	38	2	5.2	15	39.4
1947 Assali ¹	120	2	1.6	44	38.7
1948 Present series	534	1	0.18	31	5.8

We do not understand the high mortalities shown in these reports. Most of our fetal deaths were due to errors in judgment, and such should get fewer with more experience. To cite one: a gravida iii, 31 years old, was followed through an uneventful pregnancy. Due to the fact that her babies were progressively larger (8½ and 11½ pounds) it was deemed advisable to induce her before term, particularly as she was an obese person (225 pounds), making it very difficult to correctly judge the size of the baby. Accordingly, at eight and one-half months the membranes were artificially ruptured and six hours later labor began. The pains were inertial in type and after nineteen and one-half hours the cervix was dilated completely, but the head was high and the

TABLE IX. POSTPARTUM COMPLICATIONS

Endometritis	16
Retained placental tissue	11
Acute mastitis	3
Breast abscess	1
Pyelitis	3
Thrombophlebitis	2
Herniorrhaphy	2
Bronchitis, atelectasis, and pulmonary edema	5

Four hundred forty-nine patients remained in the hospital twelve days or less; sixty-three between thirteen and fifteen days, and twenty-two for a longer period. The longest period of hospitalization was twenty-nine days for a patient with a thrombophlebitis of the left leg. There were sixty-six patients with a temperature of 100.4 or over for two consecutive days, not including the first twenty-four hours post partum. Forty-five of these were febrile for only two days. Of the eighty-five patients remaining more than twelve days in the hospital, sixty-six were afebrile.

Fetal Statistics and Mortality

There were 320 male and 214 female infants delivered by version and extraction whose weights varied from 12 ounces to 12 pounds 3 ounces.

TABLE X. WEIGHT OF INFANTS

WT. IN LBS.	0-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	11-12	12 PLUS
No. of cases	5	4	16	29	115	185	134	38	2	1

Thirty-one babies were lost. Sixteen of these were stillborn and fifteen neonatal deaths. This is a gross fetal mortality rate of 5.8 per cent. There were six monstrosities, four nonviable infants (under 3 pounds), and one macerated fetus. Also, in two cases of prolapsed cord resulting in stillborns, no fetal heart sounds were heard prior to delivery, and in a case of placenta ablatio the baby was delivered by version prophylactically after the placenta had been expelled. Thus the type of delivery was of no significance in these fourteen deaths, and accordingly, the corrected fetal mortality rate is 2.6 per cent.

TABLE XI. CAUSES OF FETAL DEATH

Nonviable	4	Separation of placenta	1
Monstrosities	6	Prematurity	3
Macerated	1	Prematurity and toxemia	1
Prolapsed cord	2	Prematurity and placenta previa	1
Intracranial hemorrhage	12		

The role of version cannot be proved in the five deaths attributed to prematurity. However, since prematures tolerate any handling very poorly, it is fair to suppose that the type of delivery was contributory to the deaths of these five infants all under 5 pounds in weight.

The twelve fetal deaths due to proved or probable intracranial hemorrhage are probably attributable to the version. Versions were performed in these ten primigravidas and two multigravidas for inertia, transverse arrest, or failure of descent. The membranes were ruptured from two to twenty-six hours before delivery in all but one instance, when they were ruptured at delivery, and the average length of labor was forty-one and one-half hours, varying from ten to one hundred thirty-four hours. The average weight of the babies was 8 pounds

3. An android pelvis is the most dangerous type of pelvis for the performance of a version with regard to fetal mortality.

4. Many cases of inertia, failure of descent of the head, transverse arrest, and persistent posterior are best handled by version.

5. Premature rupture of the membranes does not contraindicate a version. The tonus of the uterine musculature and displacement of the head are the important criteria.

6. Routine mediolateral episiotomy and more frequent use of forceps to the aftercoming head are recommended.

7. Rupture of the uterus need not be a complication if gentleness and skill are practiced and contraindications to version adhered to strictly.

8. Internal podalic version and extraction is important in the armamentarium of the well-trained obstetrician. Obstetric residents should be trained in this procedure.

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position posterior. A difficult internal podalic version and extraction was done, but instead of the 8- to 9-pound baby expected the infant weighed 12 pounds 3 ounces, and resulted in a stillbirth, obviously due to intracranial hemorrhage.

There was one ruptured uterus in this series of 534 versions. Delfs and Eastman³ reports one in eighty at Johns Hopkins, and Cosgrove and associates² one in seventy-seven at the Margaret Hague. The reason for rupture in almost all cases, as in ours, is a tight ring which will not relax even with deep anesthesia, or a uterus moulded closely around the baby. Of course these are cases in which version and extraction should not be performed.

The chief contraindications to internal podalic version and extraction are:

1. Marked cephalopelvic disproportion.
2. True constriction ring dystocia.
3. A dry uterus moulded about the child.
4. Incomplete effacement and dilatation of the cervix.
5. Previous section or extensive myomectomy.
6. Placenta previa of any degree.
7. An inexperienced anesthetist.
8. Insufficient help.

Summary

A series of 534 internal podalic versions and extractions performed over a three and one-half year period is analyzed. They composed 4.1 per cent of all deliveries at the Elizabeth Steel Magee Hospital. Most of the patients were of private status, and all were delivered by or under the supervision of obstetricians, or by men with adequate training in obstetrics. Ages varied from 16 to 43 years, and gravidity from i to xvii. All but fifteen patients were of eight or more months gestation. Most of the pelves were gynecoid with the next largest category platypelloid. There were fifteen separate indications for version with the quartet of inertia, failure of descent of the head, transverse arrest, and persistent posterior the reason for 80 per cent of the versions. Over two hundred of the patients were in labor more than eighteen hours. In almost one-half of the cases the membranes were ruptured from one-half hour to five days prior to delivery. The complications of delivery included twenty-six marked physiologic retraction rings, one ruptured uterus, and seven third-degree lacerations of the perineum. Postpartum complications were not unusual, and only twenty-two of the patients remained in the hospital more than fifteen days post partum. There was one maternal mortality, and the gross infant mortality was 5.8 per cent, corrected 2.6 per cent; excluding the prophylactic versions and second twins 6.3 per cent and 3.8 per cent, respectively.

Conclusions

1. Internal podalic version and extractions should not be performed routinely.

2. There is no comparison between the dangers of breech delivery and extraction following an internal podalic version.

The residual cavity between bladder and rectum was completely closed by several purse-string sutures and suture of the vaginal mucosa. The patient was discharged after seven days. Re-examination six months later showed a completely healed vaginal vault.

The removed specimen was a flaccid sac with walls in no place thicker than $\frac{1}{2}$ cm., lined by a smooth mucosa, the arbor vitae having been entirely obliterated. The mucosa was intact except at the upper angle where it was complete but torn. Pathologic examination showed the epithelial lining to consist of a single layer of high epithelial cells with basal nuclei—typical cervix epithelium. Only close to the thinned out external os were deep-seated normal cervical glands noted.

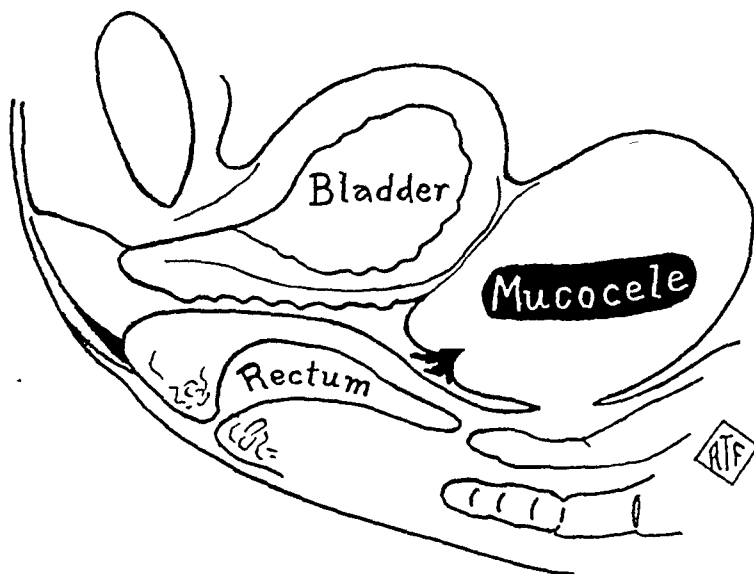


Fig. 1.—Schematic sagittal section of pelvis showing relation of distended cervical stump to pelvic viscera.

In a patient, twelve years after hysterectomy, the cervical stump, which one year previously was definitely normal in length, and had an almost obliterated canal, changed into a flaccid sac filled with clear cervical mucus and secreting mucus in large quantities. A report of the hysterectomy performed in June of 1935, received from the operating surgeon, said that the uterus was enlarged by multiple fibroids; that a supravaginal hysterectomy had been performed, both tubes and ovaries proving normal and being left in situ. The convalescence was uneventful, the patient being discharged on the fifteenth day. The patient had taken no estrogens or hormones of any kind. She did suffer from frequent flushes, although only 42 years of age. There is no explanation for this sudden change in the local situation. Evidently the somewhat stenosed canal did not permit of free drainage of the cervical mucus but what produced the sudden increase in secretion which, to my own observation, persisted at least between June 25, when I emptied the cervix by rectal and vaginal pressure, and the time of operation on July 23, when the cervix was again found to be completely ballooned, is not known. The histologic findings certainly in no way explain it.

Merits of Total Versus Supravaginal Hysterectomy

The case just presented, as well as others which I have encountered and have described,^{3, 4, 5} raises the oft- and long-discussed question of whether complete hysterectomy is preferable to supravaginal amputation with preservation of the cervical stump.

Advocates of total hysterectomy base their preference in the main, on the fact that a number of cases are reported in which carcinoma has developed in the cervical stump. Polak,⁶ as early as in 1920, was able to collect 256

MUCOCELE OF THE CERVICAL STUMP

Together With a Discussion of the Merits of Total vs. Supravaginal Hysterectomy

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NO REFERENCE to mucocele of the cervical stump could be found in a study of the literature. The amount of mucus coming from the cervix is variable and hard to measure. Viergiver and Pommerenke¹ have measured the amount of cervical mucus that could be aspirated at different times of the cycle. The maximum was from 200 to 700 mg. in weight. It is of interest that I was able to see the patient whose history follows a year before the condition to be reported had developed.

Case History

Mrs. S. K., a 41-year-old nullipara, married eight years, came to see me in March of 1946, complaining of slight postcoital bleeding which developed only two weeks before. The patient had had a hysterectomy performed in June of 1935, eleven years previously.

Examination showed a somewhat overweight woman who was somatically normal. There was a barely visible suprapubic median scar. Pelvic examination showed a nulliparous, uninfected introitus; a conical portio, the cervical stump being long, freely movable; no exudates. The adnexa could not be definitely outlined. The notation was made that the canal was almost obliterated. It did not bleed on examination or sounding. The patient was instructed to return if the bleeding recurred.

On June 25, 1947, after an interval of sixteen months, the patient was referred back to me by her physician who had been called to see her the preceding evening because the patient had expelled large amounts of clear mucus, two to three glassfuls, from the vagina. When the doctor saw her, there was still a large amount of mucus extruding. No bleeding, postcoital or otherwise had occurred since the patient had consulted me.

Her general examination was as before, the introitus nulliparous, the cervix high, the os somewhat patulous, the cervical stump seemed short, but there was a definite fluctuant resistance in the Douglas, more easily defined by rectal examination. On pressure, clear, thick mucus extruded from the external os. Introduction of a sound into the cervical canal showed a cavity about the size of an orange and was not followed by any bleeding.

The diagnosis of mucocele of the cervical stump was made, with the notation that an adenocarcinoma of the cervical canal would have to be looked for, as I had previously encountered a colloid cervical adenocarcinoma which secreted large amounts of mucus.²

On July 23, the patient was explored from below under general anesthesia, the operation consisting of an excoelation of the cervix. The vaginal mucosa at its junction with the portio was circumcised, the densely adherent bladder freed by sharp dissection. Posteriorly, the peritoneum could be pushed back until the very top of the pear-shaped mass was reached. During the manipulation, some five to six ounces of clear mucus extruded from the cervix. As the upper portion of the cervix was extremely adherent, after the canal had been split to make sure that there was no concealed carcinoma or other malignancy in the flaccid sac, the upper 1½ cm. of the musculature was left in situ with careful stripping out of the remaining mucosa.

referred to us has been followed. Our follow-up is 100 per cent. It is a fact—and I think a rather surprising fact—that *a carcinoma has never developed in a patient in whom we failed to diagnose the cancerous lesion on clinical examination or on biopsy.* There seems to me thus to be *some slight*” [all the italics are mine] “discrepancy between the experience of the cytologist and the clinician.”

In view of the above facts and observations, I continue to perform supravaginal amputation for benign lesions. Only in rare instances, if the cervix cannot be restored to a sufficient degree of normalcy, do I resort to total hysterectomy. In the presence of malignancy—corpus carcinoma or sarcoma—the radical Wertheim technique is indicated. For carcinoma of cervix, I prefer radio therapy alone, after trial of radical operation following completion of radiotherapy, without improvement of results.

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cases of stump carcinoma from the American literature. Since then, a large number of additional cases have been noted. My personal experience covers only eight cases, not one of which was operated upon by me originally. In at least of these one of which was operated upon by originally. In at least one of these,⁷ advanced carcinoma was discovered within five months of the operation, showing that the cancer had been overlooked at the time of the intervention.

It is my habit to study the cervix closely in patients in whom a hysterectomy is contemplated. Infection, erosion, polyps are dealt with appropriately so that at operation the cervix is healthy. In rare instances, normal conditions could not be restored and in these total hysterectomy was resorted to. It is my practice to cone out the upper 2 to 3 cm. of the cervical stump during supravaginal hysterectomy, thus passing the sutures, which close the stump, through cervical connective tissue devoid of mucosa. Such a procedure in itself might have prevented the formation of the mucocele just described.

In several instances I have been confronted with complete prolapse of the cervical stump. In every one of these, I have been able to obtain a permanent cure of the prolapse by means of the Manchester operation. In an approximately equal number of total eversions of the vagina following complete hysterectomy, I have been obliged to perform colpocleises to hold back the prolapse in old women, or to resort to palliation by means of the use of a Gellhorn pessary, after building up the perineum in younger patients.

Moreover, I have been consulted by an increasing number of women who complain of pain, dysuria, dyspareunia, and dryness of the genitals following complete hysterectomy. In them I find scarry, often unduly short and dry vaginal canals. I know of no means of relieving their symptoms adequately. In addition, I encounter an undue number of vesicovaginal fistulas following the total operation. I instance these sequelae because the statistically minded assure us that total hysterectomy entails no increase in mortality and but little increase in morbidity in skilled and experienced hands.

The somewhat hysterical overanxiety to ferret out cervical cancers *in situ* or often only *in prospect*, now current, is a perhaps justifiable reaction against the callous myopia, carelessness, and ignorance which for years exposed womanhood to unnecessary danger and neglect by omitting even vaginal examination because of "delicacy." Today we see the opposite picture, namely, women racked by unjustified fears, anxieties, and premonitions of disaster caused by the witch-hunter attitude of the professional cancer tracker. A careful, thorough, but less dramatic and disquieting approach is called for without deliberately alarming the woman who presents herself for her yearly checkup. Cytologic examination of the cervical and vaginal discharges is laudable if confined to competent hands. Postive findings warrant further investigation (biopsy and curettage). My interpretation of metaplastic changes is far less radical than the present ones current. In defense of my conservative attitude—if defense is necessary—I may say that my over forty years' experience coincides *exactly* with that of Dr. J. Heyman of Stockholm, Sweden, who has been in charge of the gynecologic clinic at the Radium-Hemmet since 1914, who, in a discussion of Ayre's⁸ paper, at the meeting at Atlantic City said, "At the gynecology clinic of Radium-Hemmet in Stockholm, we see a great number of patients with cancer of the uterus. We also see a great number of patients with irregular bleeding, and a number of patients are annually referred to us suspect of having a uterine carcinoma. Sweden is a sparsely populated country, and it is easy for us to follow all the patients referred to us. And we do follow them. Since 1914, any patient of the type mentioned who was

experience, there is a fairly high incidence of pelvic disease associated with cystocele. It is necessary, therefore, to operate abdominally, as well as from below, in approximately 25 per cent of the cases. For example, in the presence of an ovarian tumor, chronic diseases of the tubes, uterine fibroids, retroverted uterus in the childbearing period, etc., in conjunction with a cystocele, it is considered essential to combine a vaginal approach with an abdominal laparotomy. This double procedure taxes the patient no end, as there is considerable time lost in the preparation of the patient and surgeon in making ready for the second operation. More valuable time is lost in exposing the structures from below when these same tissues may have been partially displayed during the initial operation. For example, in doing a supravaginal hysterectomy or pan-hysterectomy, the pubocervical fascia is readily exhibited in its superior portion when the bladder is stripped off of the cervix and vagina. When a bladder retractor, is placed into position, the entire bladder floor along with Mackenrodt's ligament may be demonstrated.

The operation described in this paper is not intended to supplant any of the time-honored procedures used in the repair of cystoceles. Rather, it is intended solely for the correction of a cystocele, from within the abdomen, in those cases in which a laparotomy is imperative for the correction of other pathologic manifestations in the pelvis and it should be reserved for small or moderate-sized cystoceles. It should be done chiefly as a prophylactic measure during the course of other abdominal operations with the intention of preventing progressive dilatation of the fascial defect. It should be resorted to only under these conditions and one should refrain from applying it routinely to all types of cystoceles. In young women, in the childbearing period, who present the triad of retroverted uterus, partial prolapse, and a moderate-sized cystocele, it should be the operation of choice. One may repair the hernia by suturing the defect in the pubocervical fascia, suspend the uterus by the modified Gilliam technique, and augment the prolapse by parametrial fixation and plication of the uterosacral ligaments. All this may be done abdominally and at one session.

In abdominal cystoceleoplasty, one deals with the same structures as in any other cystocele repair; namely, the pubovesicocervical fascia. The difference, of course, lies in the fact that one approaches the structures from above instead of from below. If it is not necessary to disturb the uterus during the course of the operation, one may easily expose the same fascial structures by dividing the uterovesical peritoneum transversely along its attachment to the uterus and extending the incision out along the broad ligaments. The bladder is separated by blunt dissection from the lower segment of the uterus, the cervix, and the vagina. This is facilitated by using a sponge stick and gradually stripping the bladder away from its attachment to the genital tract practically to the urogenital diaphragm. Tugging on the uterus or cervix in an upward fashion causes tension on the anterior wall of the vagina and pulls the urethra from under the pubic bone. In this manner, dissection and mobilization of the neck of the bladder may be done expediently. A narrow bladder retractor is used to elevate the bladder and the pubocervical vesical fascia along with the pillars or lateral ligaments of the bladder are easily disclosed. The thickened portions of the pubocervical fascia lying along the anterolateral portions of the vagina are grasped with Allis clamps and brought together with interrupted No. 1 chromic catgut sutures. These are placed consecutively in such a manner as to approximate the fascia in the midline and obliterate the hernial defect. Traction on each successive suture facilitates exposure. They should be placed progressively and extend as far forward as possible to the posterior surface of the

ABDOMINAL CYSTOCELEOPLASTY

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A CYSTOCELE may be defined as a true hernia of the bladder through the pubocervical fascia and anterior wall of the vagina. These layers between the vagina and bladder are important in forming a hammock for the bladder and the disruption of this eventually leads to a cystocele. This is usually caused by the prolonged stretching of the vagina and its covering beyond its threshold of resilience during parturition and the fascia remaining permanently relaxed. The thinned attachment of the pubocervical ligament may be torn completely from the cervix. It is at this point where the majority of cystoceles observed protrude through the fascial barrier near the attachment of the cervix and at the proximal part of the vagina.

In its early stage, the cystocele is usually rather small and customarily, solitary in nature. However, if one should intelligently evaluate the potentialities, he would find that the cystocele may become progressively larger with age. The etiological factors mainly responsible for the progressive development of the hernia are the increased intra-abdominal pressure resulting from defecation and urination and the gradual decrease in tonicity of the ligaments which occurs with the climacteric. As a person becomes older, the ligaments become more lax and flaccid, and yield to stress and strain much more easily. If this process continues long enough, the entire length of the pubocervical fascia becomes involved, and when the area in the region of the neck of the bladder yields, it gives rise to an urethrocele. If one could correct the defect in its early stages, he might easily prevent the formation of a large cystocele with a complicating urethrocele in later life. Ordinarily, one would not attempt to repair a small or moderate sized cystocele from below, as usually it does not cause any symptoms at this time. Secondly, the procedure is often rendered difficult because of its inaccessability due to the high fixation of the cervix. Normally, the gynecologist undertakes correction of the cystocele when it has become rather large and is the cause of troublesome urinary symptoms such as stress incontinence, frequency, urgency, etc. Any procedure which repairs the rent in the pubocervical fascia, thereby creating a strong bladder floor, will remedy the cystocele. Everyone concedes that this is most easily accomplished by the vaginal route in the large baggy types of cystoceles complicated by a urethrocele. Also, there is no doubt that the Manchester type of vaginal repair restores the structures more nearly to their anatomic position than any other type of procedure. Operations, such as suspension of the uterus, hysterectomy, shortening of the round ligaments, ventral fixation, etc. do not correct the cause of the hernia and are used injudiciously. Many authors add that cystoceles can be repaired only from below. It can be wisely stated that in the majority of cases this is quite true, as usually the gynecologist is not consulted until the hernia is quite large and is causing annoying symptoms.

Frequently, however, one is confronted with a patient who has a valid indication for an abdominal operation and has also a small to a moderate-sized cystocele. This multiplicity of pathologic conditions is not unusual and, in my

neck of the bladder. Parametrial fixation of the cardinal ligament of Mackenrodt may also be carried out with little difficulty. A mattress suture of No. 1 chromic catgut is placed in the parametrium on each side of the cervix in such a fashion that when the suture is tied, it fixes the condensation of fascial fibers anterior to the cervix. This procedure shortens the overstretched cardinal ligaments and overcomes the partial prolapse of the uterus. If additional support is needed, the uterosacral ligaments may be plicated to add further strength to the supporting structures. By this method, a moderate-sized prolapse may be corrected effectively and practically. The entire area is then peritonealized with the uterovesical peritoneal flap, either in a manner following a hysterectomy if the uterus was removed, or in a manner similar to the peritonealization used during a low cesarean section.

One is certain to ask what happens to the puckered vaginal mucosa after the vagina is narrowed from side to side. In my experience, the redundant vaginal wall retracted and involuted in six to eight weeks. This was due evidently to the rather elastic nature of the vaginal wall which contains involuntary muscle fibers in addition to fascia. Apparently, these fibers contract and, after a short period of time, the normal contour of the vagina is restored. There are several conditions which might interfere considerably with the operative technique. Obesity of patients or extremely deep pelvis may prove to be almost unsurmountable obstacles and impede efficacious completion of the operation. Also, one should not attempt to correct a large cystocele complicated by an urethrocele which presents symptoms of stress incontinence. Exposure of the vesical neck is usually rather difficult and plication of the urethral sphincter is an impossibility.

Conclusions

1. Cystoceleoplasty by the abdominal route is not only feasible but the results are entirely satisfactory and compare favorably with other cystocele repairs.

2. The operation can be performed without much difficulty while repairing other pathologic conditions in the pelvis and much time can be saved by adopting this procedure.

3. Moderate degrees of prolapse of the uterus may be corrected concurrently by shortening the cardinal and uterosacral ligaments.

4. Certain conditions such as obesity, extremely deep pelvis, or large cystoceles with complicating urethrocele and symptoms of stress incontinence may be considered valid contraindications for the performance of the operation.

CASE 1.—M. A., aged 36 years, was admitted to Harford Memorial Hospital on Jan. 7, 1948, complaining of pains in the lower abdomen, irregular menstrual periods, a sense of pressure in the pelvis, and a feeling as if everything were falling out. General physical examination was essentially negative. Examination of the abdomen revealed it to be flat; liver, spleen, and kidneys not palpable. There was a lower right rectus well-healed scar. Moderate diffuse tenderness was noted in both lower quadrants; no rigidity or palpable masses. Examination of the pelvis disclosed the external genitals to be normal; Bartholin's and Skene's glands not palpable. The outlet was marital, multiparous with moderate relaxation of anterior vaginal wall and slight relaxation of posterior vaginal wall. The cervix descended somewhat on straining and appeared healthy. The uterus was normal in size, shape, position, and contour. Both adnexa were somewhat enlarged, fixed, and tender. The pre-operative diagnosis was chronic pelvic inflammatory disease, (bilateral), cystocele (moderate), and prolapse of the uterus (first degree). Laparotomy was done on Jan. 8, 1948, and the

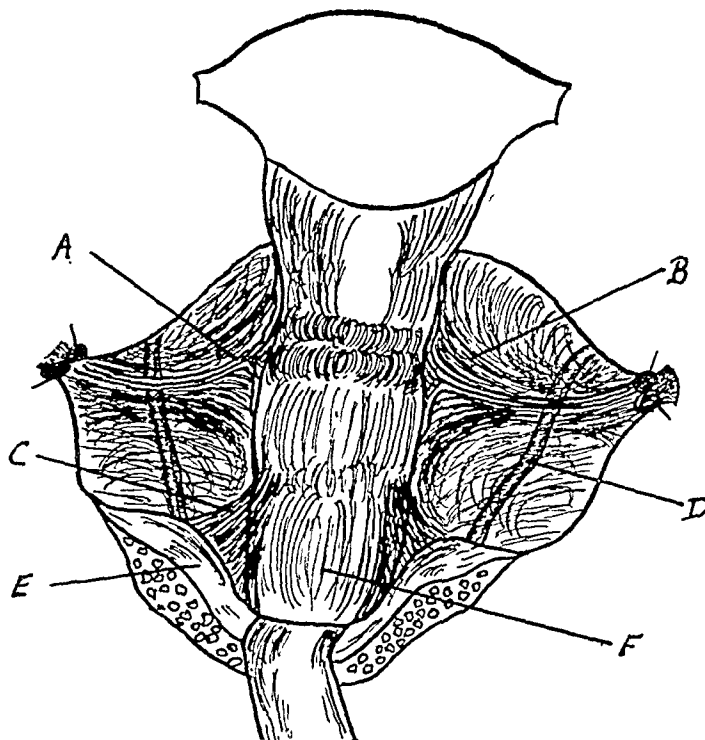


Fig. 1.—Schematic drawing showing exposure after vesicouterine peritoneum and bladder is stripped off the uterus, cervix, and vagina. A-Uterine vessels. B-cardinal ligament. C-Lateral ligaments of the bladder. D-Relative position of ureters. E-Bladder. F-Pubocervical fascia.

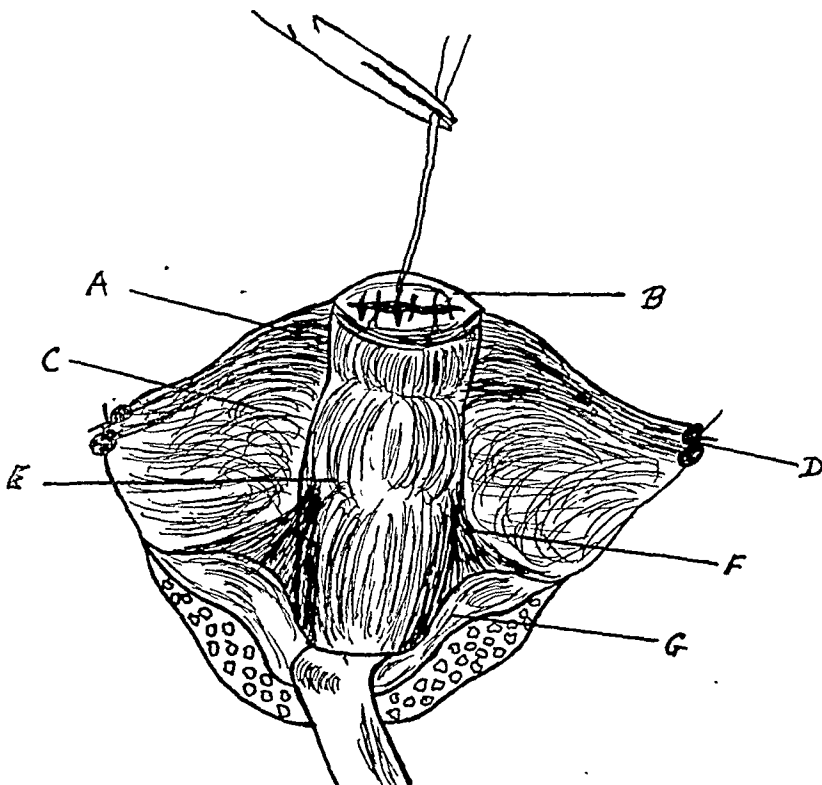


Fig. 2.—Schematic drawing showing exposure during a supravaginal hysterectomy. A-Cardinal ligaments of Mackenrodt. B-Cervix. C-Parametrium. D-Stumps of round and broad ligaments. E-Pubocervical fascia. F-Lateral ligaments of the bladder. G-Bladder.

uterus was found to be normal in size, shape, and position. Both tubes were convoluted, dilated, clubbed, and fixed to the broad ligament. The ovaries were essentially normal. The appendix had been previously removed. A bilateral salpingectomy and an abdominal cystoceleoplasty were done along with parametrial fixation of the cardinal ligaments and plication of the uterosacral ligaments. The postoperative course was afebrile after the second day and the patient was discharged on the seventh day in good condition. Pelvic examination after six weeks revealed the vaginal wall normal in contour and there was no bulging on bearing down. The sense of pressure in the pelvis was no longer present and the patient stated that she felt quite well.

CASE 2.—P. H., aged 24 years, was admitted to Harford Memorial Hospital on Jan. 14, 1948, complaining of pains in the lower portion of the back and continuous bleeding of twelve weeks' duration. This had varied from a profuse reddish brown discharge to a bright red free bleeding. General physical examination was essentially negative. The abdomen was flat; liver, spleen, and kidneys not palpable. There was moderate diffuse tenderness in the lower abdomen, especially over McBurney's point; no rigidity or palpable masses. Examination of the pelvis disclosed the external genitals to be normal. The outlet was marital, multiparous with moderate relaxation of anterior vaginal wall. The cervix appeared slightly hypertrophied but healthy in appearance. The uterus was slightly enlarged and moderately irregular. It was noted that the right adnexa were slightly enlarged and tender. Left adnexa negative. The preoperative diagnosis consisted of uterine fibroids (small), chronic appendicitis, and cystocele (moderate). A dilatation and curettage were done and the body cavity of the uterus was found to be rather irregular. On laparotomy, it was noted that the uterus was enlarged and the contour was slightly lobulated. Both tubes were normal. The right ovary contained a corpus luteum. The left ovary was normal. Since the patient had three children and since the question of further childbearing was unimportant, a supravaginal hysterectomy was done. Following this, an abdominal cystoceleoplasty with plication of the uterosacral ligaments was carried out. The appendix was about 7 cm. long, moderately injected, and bulbous at the tip. This was removed in the routine manner. The postoperative course was uneventful and the patient was discharged on the eighth day in good condition. Pelvic examination after six weeks revealed the cervix to be well supported and the anterior vaginal wall was smooth, firm, and well bolstered.

CASE 3.—M. M., aged 35 years, was admitted to Bon Secours Hospital on Feb. 8, 1948, complaining of pain in the right lower quadrant, and intermittent attacks of nausea. During the past two years, she complained of frequency and urgency with inability to empty the bladder completely. Patient had a nephropexy done one year ago without relief of symptoms. General physical examination was essentially negative. The abdomen was normal, liver, spleen, and kidneys not palpable. There was a right well-healed kidney scar. Moderate tenderness was noted over McBurney's point; no rigidity or palpable masses. Examination of the pelvis disclosed normal external genitals. The outlet was marital, multiparous with moderate relaxation of anterior vaginal wall. The cervix was small and slightly eroded. The uterus was found to be retroverted (second degree); both adnexa were prolapsed but neither were enlarged nor tender. The preoperative diagnosis was retroverted uterus (second degree), chronic appendicitis, and cystocele (moderate). A laparotomy was performed on Feb. 9, 1948, and it was noted that the uterus was partially retroverted with both adnexa prolapsed. There was a slight descensus of the pelvic organs. An abdominal cystoceleoplasty with parametrial fixation was done by the usual technique, after which, a modified Gilliam hysteropexy with plication of the uterosacral ligaments was carried out in the customary manner. The appendix was moderately injected throughout and the distal half was rather thick walled and contracted. This was removed and the stump inverted by pursestring. The postoperative course was essentially uneventful and the patient was discharged on the tenth day in good condition. Examination after six weeks revealed the bladder to be well supported and the mucous membrane of the anterior vaginal wall had involuted completely. Patient was symptom free and felt quite well.

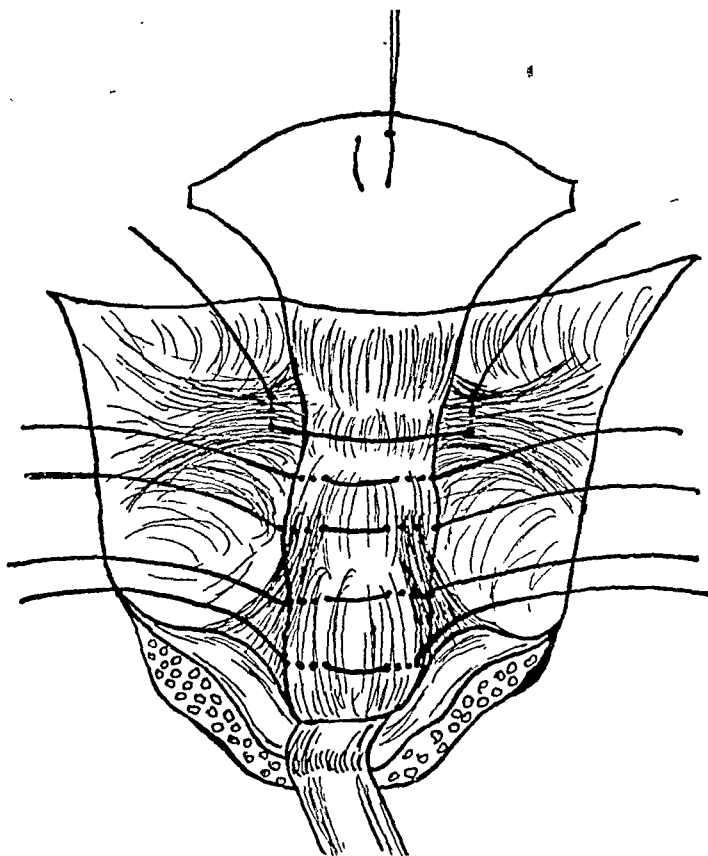


Fig. 3.—Schematic drawing showing interrupted sutures placed in the pubocervical fascia on the anterolateral portion of the vagina. A mattress suture has been inserted into the cardinal ligament on each side of the cervix.

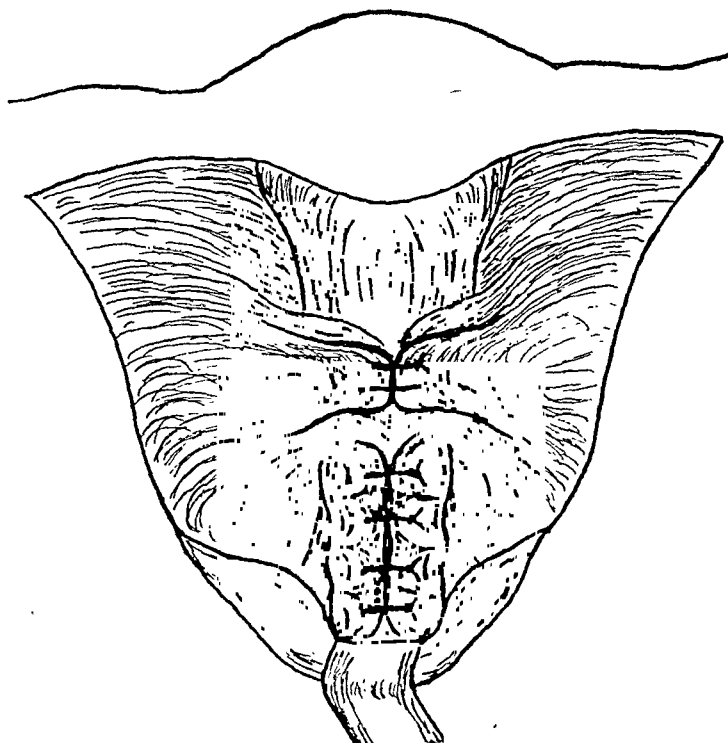


Fig. 4.—Schematic drawing showing the cardinal ligaments fixed anterior to the cervix and the pubocervical fascia plicated in the midline..

which grasps and lifts the lower uterine segment against the spinal column and if another hand compresses the fundus, with or without massage (usually without), it will be a matter of a few minutes until retraction of the uterine fibers will occur, bleeding will stop, and the uterus and cervix will return to normal. Vigorous massage and compression in ante flexion or continuous massage on the uterus which is already firm do more harm than good.

Sewell and Coulton speak of "Manual Removal of the Placenta, as a Benign Procedure." They stated, "Not many years ago, manual removal of the placenta was considered one of the most deadly and dangerous procedures that obstetricians could be called upon to perform and the average mortality ranged from 10 to 15 per cent."

TABLE I. MANUAL REMOVAL OF PLACENTA

REPORTED BY	TOTAL DELIVERIES	TOTAL MANUAL RE-MOVALS	PER CENT INCIDENCE	PER CENT MATERNAL MORTALITY	PER CENT MATERNAL MORBIDITY
L. D. Odell and W. F. Hovis, Iowa City, Surg., Gynec. & Obst. 77: 553, 1943.	15,824	70	.25	2.8	----
Dawson, Univ. Otago, New Zealand, M. J. 43: 7, 1944.	6,000	40	.66	2.5	5
Schwartz and Richards, Bellevue Hosp., AM. J. OBST. & GYNEC. 45: 235, 1943.	8,902	74	.83	2.7	43.1 Uncorrected
J. L. Ahumada and J. Diradourian, Arch. Clin. obst. y. ginec. "Eliseo Cantón" 1:200, 1942.	5,280	702	1.3	8.1	----
J. P. Clerc, Univ. Geneva, Gynecologia 121: 213, 1946.	6,973	100	1.4	0	14 Corrected
R. E. Arnell and R. F. Phillips, Charity Hosp. of Louisiana, South. M. J. 34: 598, 1941.	-----	152	---	6.5 Gross 1.9 Corrected	----
C. H. Peckham, Bull. Johns Hopkins Hosp. 56: 224, 1935.	From 1896 to 1933	186	1.2	10.76 if operative del'y, 4.48 if spontaneous	48.48
A. Montag, Monatschr. f. Geburtsh. u. Gynäk., Feb., 1926.	15,100	147	1.02	4.76	10.45 30.6
W. J. Dieckmann et al., Chicago Lying-in Hosp., AM. J. OBST. & GYNEC. 54: 415, 1947.	6 months, 1946 6 months, 1945	80 18	--- ---	0 0	7.9 9.2

It has been claimed that the more infected the patient was at the time of removal, the greater the danger of manual removal. Is this actually true? This has not been my experience. Waters and Norton and others, who remove the placenta manually in their extraperitoneal cesarean sections in patients already infected do not report that the procedure is risky. If it is not a dangerous procedure to remove the placenta in frankly infected cases that are subjected to the extraperitoneal operations, why should there be any greater danger in removing the placenta vaginally? Is it not logical to suppose that the operative procedures which are used to remove the fetus together with the blood loss incurred from trauma increase the incidence of sepsis, rather than the manual removal of the placenta itself?

THE THIRD STAGE OF LABOR A PLEA FOR MANUAL REMOVAL OF THE PLACENTA

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THE third stage of labor has repeatedly been the subject of much discussion and dissension, yet is the least understood and most ill managed and the most tampered-with stage. We are told that the persistence of postpartum hemorrhage is due to mismanagement of the third stage and that most deaths are preventable. If our teachings have been at fault, surely this can be corrected.

The practice of massaging and squeezing the uterus after the birth of the baby to separate the placenta, as well as the less traumatic plan of holding the fundus are mentioned only to be condemned. By such procedures, nothing is gained and much is lost by unnecessary traumatism. They may result in partial detachment of the placenta with more bleeding, hence it is far preferable to wait for clinical signs of separation than to hasten it by Credé's compression. The ecchymotic and contused abdominal walls, the sensitive and bruised uterus, and the relaxed and tender uterine ligaments are familiar observations. There is little wonder that manual removal of the placenta under such circumstances carried a bad reputation. Paddock calls our attention to the fact, "modern methods of amnesia, analgesia and anesthesia tend to make the third stage unphysiologic. . . . It takes longer for the patient to marshall her normal powers of response. The uterus is flaccid and will not respond to stimulation quickly. Hence, any attempt to separate or remove the placenta would be expected to result in increased bleeding, without the normal hemostatic effect of the contractile uterus." While the writer does agree that general anesthesia and large doses of sedatives do delay the speed of placental expulsion, and even in some cases interfere with its completeness, he feels that Ergotrate, properly timed, and given intravenously as soon as the baby's head is born, and given in large doses (i.e., never less than 1/160 grain), restores the mechanism of uterine contractability to normal within a matter of 20 to 30 seconds.

It must be remembered that the placenta, even under deep anesthesia, separates by itself very shortly after the baby is born. Its expulsion, however, under general anesthesia, is delayed, hence it is obvious that anesthetized patients must be given an oxytocic. The writer feels that if the empty uterus is immediately lifted high out of the pelvis by pressure through the anterior abdominal wall and the elevated uterus is held in this position by a hand

move the placenta is freely lubricated with tincture of green soap. The parturient canal is carefully checked for lacerations, tumors, uterine inversion, etc. The position, degree of placental separation, and denseness of placental adhesions are noted as the placenta is removed. In only 16 cases (1 per cent), was the placenta found completely separated and loose in the vagina. In all others, the placenta was still attached to the uterus. However, in 408 cases (25.1 per cent), the lower placental edge was partially separated for a distance of one to two inches. It is evident that all of these cases required further manual separation of the placenta to complete the process.

An analysis of Table II shows the maternal morbidity reported by the writer as zero. The puerperal morbidity for the 1,625 cases was 4.6 per cent. Since the writer could not find a single case where the procedure of manual removal of the placenta was responsible for the puerperal morbidity, this figure of zero seems justified.

In the writer's experience, routine manual removal of the placenta has reduced the incidence of postpartum hemorrhage, has decreased the incidence of delayed puerperal hemorrhages (5 to 21 days post partum), has kept blood loss at a minimum, has not increased the incidence of puerperal morbidity, has made the operator the master of the third stage, not its timid observer, has enabled careful exploration of the uterus; has not been accompanied by a single case of uterine inversion; and has prepared for the packing of those rare uteri which continue to bleed after placental separation—i.e., abruptio placentae, placenta previa, pathologically adherent placentas, etc. By careful exploration at this stage, one can detect placenta increta, submucous fibroids, uterine, cervical, and vaginal tears requiring sutures, constriction rings, threatened uterine rupture or inversion, undiagnosed twins, etc. The writer has been able to check up on the statement that "a patient who has had one manual removal of the placenta is likely to require another removal in subsequent pregnancies." This statement I have found to be correct. The placenta is not infrequently more densely adherent in subsequent removals, but not always. I have also been impressed by the increase in the delay in the third stage of labor in many cases of prematurity and immaturity of the infant and maceration of the fetus. Twin placentas by their huge size are often a cause of delayed third stage. It may also be stated that the larger the weight of the baby and placenta or the area of maternal surface of the placenta, the greater the loss of blood. An exception to this is the larger edematous placenta of hydrops fetalis. It has also been my finding that difficult operative procedures, prolonged labors, and amnion sac infections cause delay in the third stage of labor. Placental abnormalities, i.e., tubocornual placentas, bilobate, membranacea, succenturiata, etc., have also been responsible for delayed placental stage. While all these factors are important, I have been impressed by the fact that, in the majority of the cases where I have been called in consultation, mismanagement of the third stage, with resulting hemorrhage and placental retention due to constriction ring of the uterus, has been the commonest cause. In these cases, morbidity was directly related to the degree of hemorrhage and shock.

Comment

The purpose of this paper is to enter the plea for earlier manual removal of the placenta. It is my conviction that the procedure of manual removal of the placenta has been unfairly condemned. The bad results of this procedure have been measured by the worst emergencies for which it is undertaken,

Obstetricians are now teaching earlier manual removal. Stoeckel taught, "Manual removal of the placenta should be done earlier and more frequently than it has been done." Greenhill remarks, "The evil consequences of manual removal of the placenta are usually due to procrastination. In hemorrhage, due either to uterine atony or laceration after delivery of the baby, the placenta should be removed without delay and not after the patient has lost too much blood." If an obstetrician knows and practices proper asepsis, he can safely invade the cavity of the uterus.

Marked differences of opinion by experts only confuse the students. It is my opinion that if students were taught immediate manual removal of the placenta with strict attention to asepsis and gentleness, much blood could be saved in those cases that are already under anesthesia.

Dieckmann has been advocating manual removal of the placenta for many years and he recently reported 80 manual removals of the placenta and 12 explorations of the uterus for a six-month period in 1946, which he compared with 18 manual removals and 2 explorations done during a similar length of time in 1945, and found that the hospital morbidity was 7.9 per cent in 1946 and 9.2 per cent in 1945. He stated, "We believe that the only way to learn to remove the placenta manually is to do it in normal cases under supervision." The dicta that "the only safe uterus is an empty uterus," that "the empty uterus will not bleed," that "the time to stop a postpartum hemorrhage is before it begins," that "the uterus can be invaded safely when this is performed aseptically," and that, other things being equal, "a short third stage should have less blood loss than a long third stage" have been responsible for the writer's unorthodox practice of immediate manual removal of the placenta in all of his last 1,625 anesthetized patients. All of the cases reported have been delivered by the writer at the Columbus Hospital in Newark, New Jersey.

TABLE II. TOTAL NUMBER OF CASES—1,625

1. Forceps	818
Number deliveries, full term	602
Premature, 7 to 8½ months	65
Version and breech extraction	21
Breech extraction	75
Twins	26
Erythroblastosis	4
Dührssen's incisions	2
Face presentation	5
Anencephalus	4
Hydrocephalus	1
Transverse presentation	2
Total	1625
2. Maternal mortality	0
3. Maternal morbidity	0
4. Number requiring tamponade	3
5. Number of placenta found adherent	7
6. Number of delayed postpartum hemorrhages, 5 to 21 days	4
7. Number requiring transfusions for postpartum hemorrhage	None

The technique utilized does not differ from the classical descriptions given by most textbooks. Immediately after the delivery of the baby, the gloved hands are thoroughly soaked in a weak Lysol solution. The hand used to re-

SPECIFIC ESTROGENIC AND ANDROGENIC SMEARS IN RELATION TO THE FETAL SEX DURING PREGNANCY*

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IN A STUDY of vaginal spreads from some 2,500 women, it appeared that cytolysis was an estrogenic effect while the presence of mucoid material with increased cornification indicated androgen activity. A survey of 253 pregnant women during all stages of pregnancy revealed a close correlation of the androgenic and estrogenic smear to the fetal sex.⁷

The evaluation of estrogenic activity by the vaginal smear is based on the amount of cornification present.¹⁻⁵ The frequent occurrence of spreads with increased numbers of Döderlein bacilli or complete destruction of cytoplasm has been intriguing. Little attention has been paid to the presence of mucoid material.

The purpose of this paper is to present data on a new series of 89 pregnant women, in whom vaginal smears were taken at various stages of pregnancy.

Method of Investigation

Vaginal smears were taken in 89 women during various stages of pregnancy. Desquamated cells from the vaginal epithelium were obtained by insertion of a cotton applicator into the vault of the vagina. The staining procedure employed was that of hematoxylin and carmine for the additional evaluation of glycogen.

Results

The effect of pregnancy on the vaginal epithelium is essentially a progressive increase in proliferation and glycogen deposition, due to augmented estrogen production. Increased progesterone activity causes more rapid desquamation of epithelial cells. The vaginal smear at any time during pregnancy will thus reflect the state of estrogen-progesterone activity. The main characteristic changes in the smear are a progressive increase in the number of cells with decrease in size and increased glycogen deposition. The nuclei are at first relatively large, round, vesicular, then tend to become oval shaped and then appear as elongated rod-shaped pyknotic nuclei. The term "luteal cells" has been suggested for cells containing such nuclei, since they occur in moderate numbers during the luteal phase. Polymorphonuclear leucocytes are usually present during the early phases of pregnancy and tend to disappear soon after the twelfth week (Figs. 1 to 4). Not infrequently, however, smears with predominantly polymorphonuclear leucocytes are found also during the later stages of pregnancy, but are without significance as to the course of gestation. The characteristic changes of later pregnancy, consisting of very large clusters of small luteal cells with a high glycogen content (Fig. 4), may be frequently found also during the earlier stages. Vaginal smears are thus unreliable for the evaluation of the phase of pregnancy.

*Aided by a grant from Ayerst, McKenna and Harrison, Ltd., New York, N. Y.

hence its reputation as a serious operation. It is my belief that the routine and immediate removal of the placenta in the already anesthetized patient is a harmless and rational procedure when performed by men adequately trained in its performance. In the past, we have suffered from too rigid an interpretation of the indications for removal. More radical liberalization of indications for manual removal of the placenta are in order. I do not expect that most obstetricians will agree with my practice, but I feel that a more generous resort to the procedure recommended will greatly reward those who are bold enough to try it. A word of caution is necessary. Until this practice of mine has been thoroughly checked by several major maternity hospitals, I would not recommend its general use by the average practitioner. In the hands of men properly trained, immediate routine manual removal of the placenta in the anesthetized patient is a safe practice.

Conclusions

One thousand six hundred twenty-five cases of manual removal of the placenta performed by the writer in his private practice are reviewed. The mortality of the procedure was zero. The morbidity was no higher than that seen in normal vaginal deliveries without resort to removal of the placenta. Because of prompt removal of the placenta, the uterus contracts more quickly and firmly. The blood loss was less than that seen where compression and expression of the uterus were resorted to. The number of cases requiring uterine tamponade has decreased considerably since this practice was followed. The procedure of manual removal of the placenta is still notoriously bad in its results when performed on the shocked and exsanguinated patient.

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Fig. 3.—Twentieth week of pregnancy. Note decreased cellular size with increased folding, elongation of nuclei, and absence of polymorphonuclear leucocytes.



Fig. 4.—Thirty-sixth week of pregnancy. Note the increased number of cells of smaller size with increased number of rod-shaped nuclei of the so-called luteal cells.

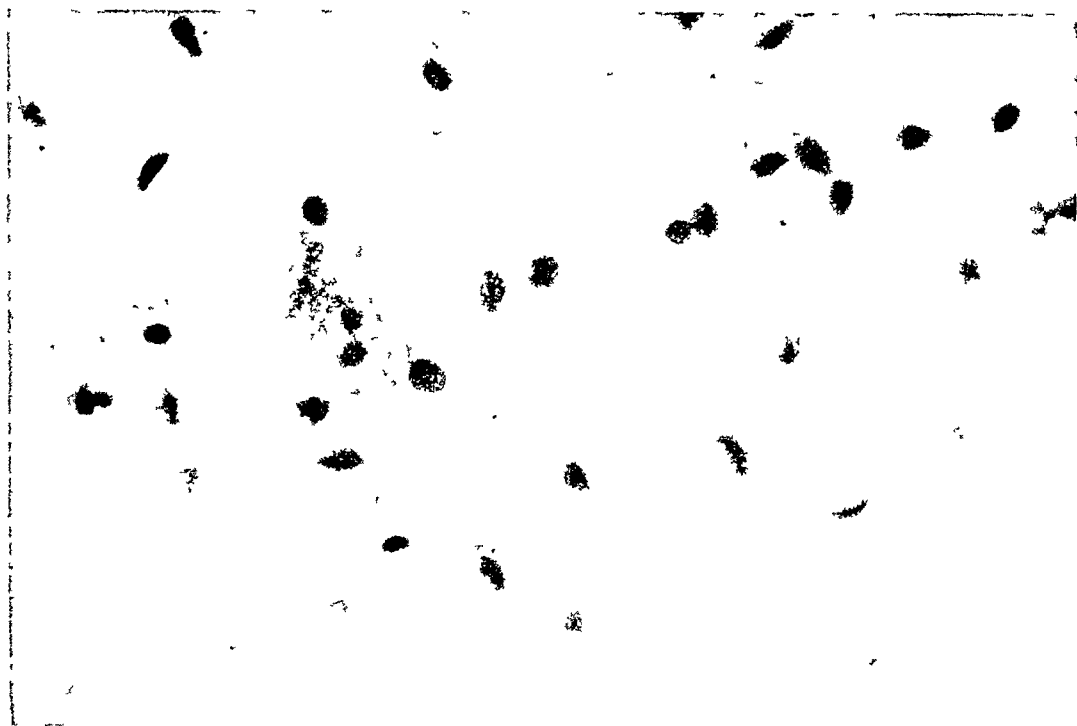


Fig. 1.—Early pregnancy. Accentuation of the luteal phase.

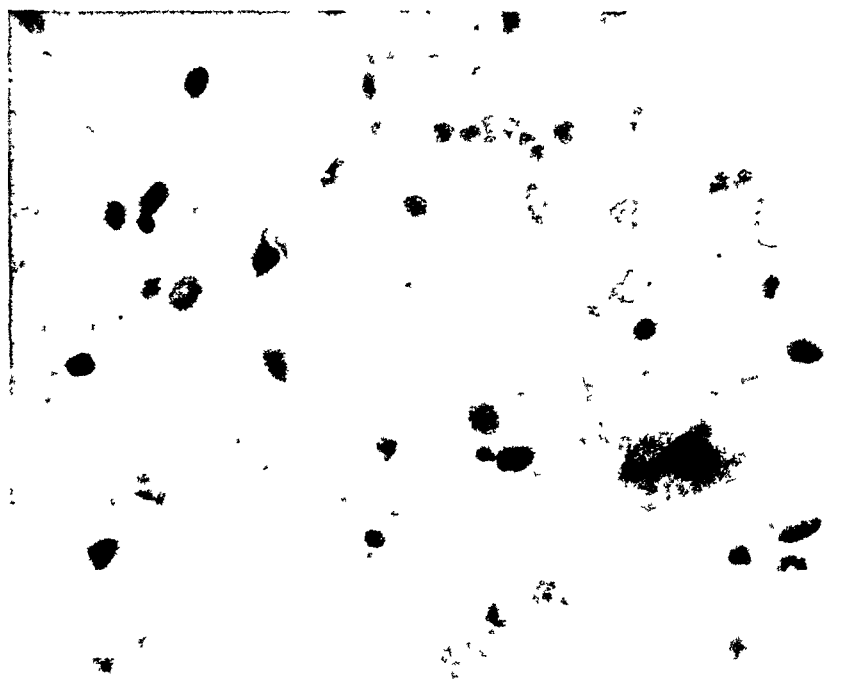


Fig. 2.—Tenth week of pregnancy. Note especially the large cells with large, round, vesicular nuclei. There are polymorphonuclear cells and small numbers of Döderlein bacilli.

In addition to these progressive changes, three specific types of smears are frequently encountered. Each of these presents features identical to those found in menstrual disturbances and other endocrine disorders.

The cytolytic smear is characterized by a large number of Döderlein bacilli with almost or complete destruction of cellular cytoplasm. The nuclei, usually relatively large, round, or oval and vesicular, are intact and there is usually evidence of increased estrogen activity, such as single cornified cells and free rod-shaped pyknotic nuclei of destroyed luteal cells (Fig. 5).

There are two types of androgenic smears. The mucoid cornified smear consists of fully cornified cells and abundant mucoid material. Döderlein bacilli or leucocytes are not found in association with this smear (Fig. 6). The glycolytic type is the other androgenic smear and shows extracellular glycogen with cellular glycopenia (Fig. 7).

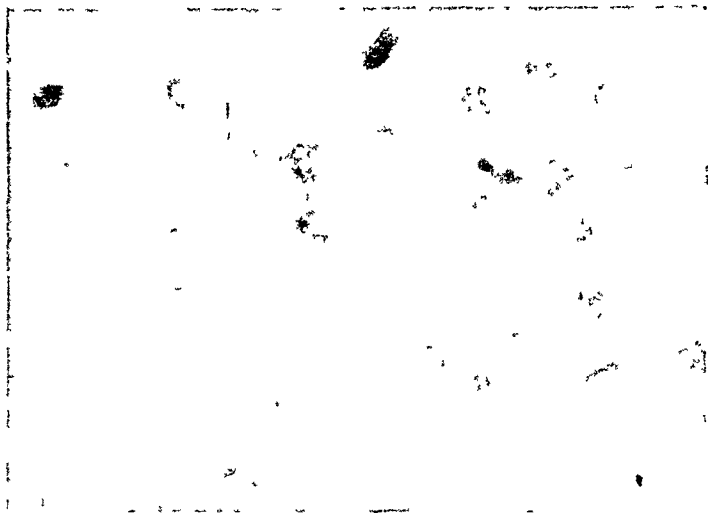


Fig. 7.—Glycolytic smear. There is cellular glycopenia with extracellular location of glycogen.

TABLE I. SPECIFIC ESTROGENIC AND ANDROGENIC SMEARS IN RELATION TO THE FETAL SEX

STAGE OF PREGNANCY (WEEKS)	TYPE OF SMEAR	SEX PREDICTED	SEX DELIVERED
16	C	Female	Female
18	C	Female	Female
18 and 24	C	Female	Male*
19	MC	Male	Male
19	EG	Male	Male
20	MC	Male	Male
22	C	Female	Female Twins
22	C	Female	Female
24	C	Female	Male*
24	C	Female	Male*
27	MC	Male	Male
27	C	Female	Female
28	MC	Male	Male
28	MC	Male	Male Twins
28	C	Female	Female
32	C	Female	Female

C—Cytolytic (estrogenic) MC—Mucoid cornified (androgenic) EG—Extracellular glycogen (androgenic) *—Error

The determination of the fetal sex was attempted only with such specific smears between the sixteenth and thirty-second week of pregnancy. In the presence of a cytolytic smear, a female fetus was diagnosed, while a male infant

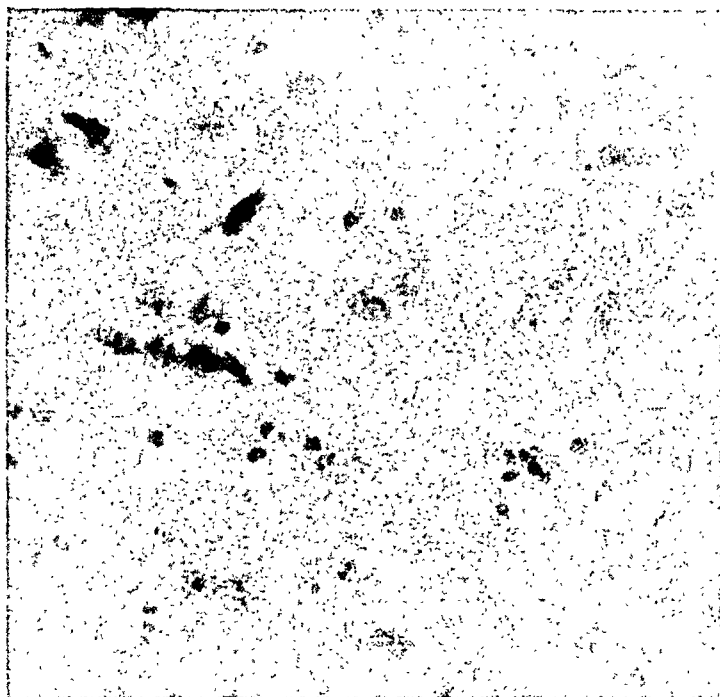


Fig. 5.—Cytolytic smear. Note the complete destruction of cellular cytoplasm. The nuclei are free and intact and there is a large number of Döderlein bacilli.

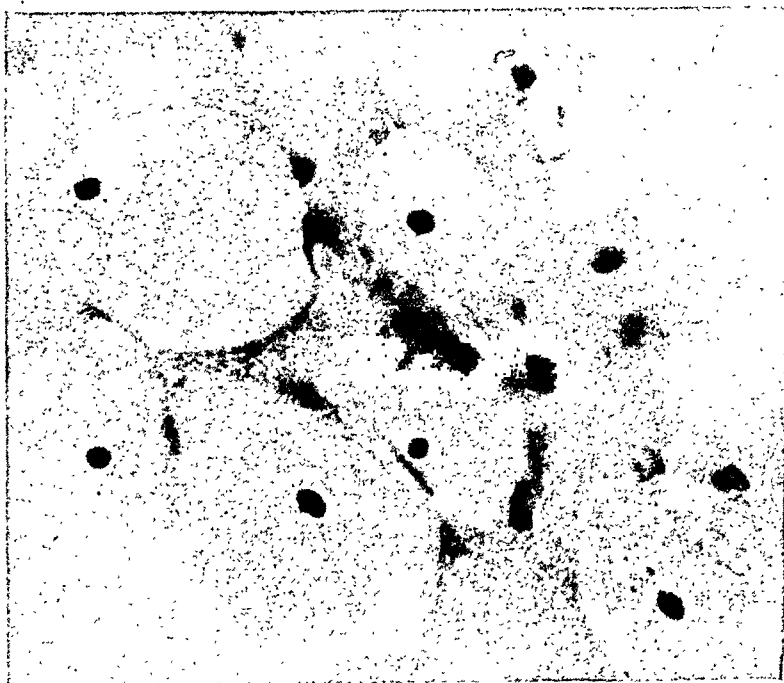


Fig. 6.—Mucoid cornified type of smear. Most cells are fully cornified. The dark substance surrounding and covering the cells is mucoid material.

dence of estrogen activity. The Döderlein bacillus is viable only in an acid medium at a pH of 3.8 to 4.4, which apparently is due to a high estrogenic level.⁸ During the menopause, when estrogen activity declines, the pH rises. The free rod-shaped nuclei of destroyed luteal cells, usually associated with cytolysis, are an additional sign of estrogen activity, since they occur, due to increased crowding of cells, in the presence of marked proliferation of the vaginal epithelium. Frequently, the presence of a number of intact cornified cells points to good estrogen production.

The androgenic, mucoid, cornified type of smear was found on androgen therapy and in conditions where a shift in the estrogen-androgen ratio had occurred toward an absolute or relative increase in androgens.⁶ The combination of cornification with mucification is probably due to the fact that androgens inhibit the effect of progesterone on the vaginal epithelium, thus preventing the rapid desquamation of cells and thereby allowing the cells to mature to complete cornification under the effect of estrogen. The glycolytic smear is very rare. In a series of 253 pregnant women, it occurred in only eight and was in all cases associated with a male infant.⁷ In about 2,500 nonpregnant women, it was seen in only four and was due to conditions of increased androgen activity. In the present series it occurred in only one woman and was followed by the birth of a male infant. The close relationship of such specific estrogenic and androgenic smears to the fetal sex is in accordance with earlier observations and supports the recent findings on the relationship of blood gonadotropins to the sex of the fetus.⁹⁻¹¹

The extremely low incidence of specific smears during pregnancy limits the value of the vaginal smear method as a means for sex determination. The results, however, indicate that the maternal hormone levels change in accordance with the fetal sex. The source of the particular increased hormone is probably the fetus itself and the cases which either fail to show these specific changes or give errors may be explained by the fact that the maternal hormones may mask those of the fetus. It is interesting to note in this connection that all three errors occurred with estrogenic smears. Furthermore, the greatest percentage of specific smears is found between approximately the eighteenth and twenty-sixth weeks of pregnancy. After this, smears usually show the normal changes of advanced pregnancy. Gonadotropin assays during the eighteenth to twenty-sixth week of pregnancy have shown a greater percentage of specific reactions with a higher percentage of accuracy.¹¹

Five women showed smears consisting of polymorphonuclear leucocytes only and seven women presented smears with immature or basal cells.

The more definite outcome of this investigation is the knowledge gained on the normal changes and variations of vaginal smears during pregnancy. All types of smears can be found during normal pregnancy. The finding of increased cornification in three cases followed by abortion is interesting in this connection and confirms a previous report.¹²

was predicted on the basis of a mucoid cornified or glycolytic smear. Out of 86 normal pregnancies, specific spreads were obtained in only 22 women. At the time of writing this report, 16 have been delivered and, of these, the sex of the fetus was accurately predicted in 14, or 87 per cent (Table I).*

It is interesting to note that, in the case of female twins, the smear was markedly cytolytic, while the male twins were accompanied by a very intense mucoid cornified smear. The three errors occurred with the estrogenic smear.

In six cases, smears with an increased number of cornified cells without mucus were found and three patients aborted shortly after the appearance of this type of smear (Fig. 8).

It was found that pregnant women who show the typical late pregnancy changes in early phases of pregnancy (Fig. 4) are usually delivered of female infants. Seven women in this series showed between the sixteenth and twenty-fourth weeks advanced pregnancy changes and six, or 83 per cent, were delivered of female infants (Table II).

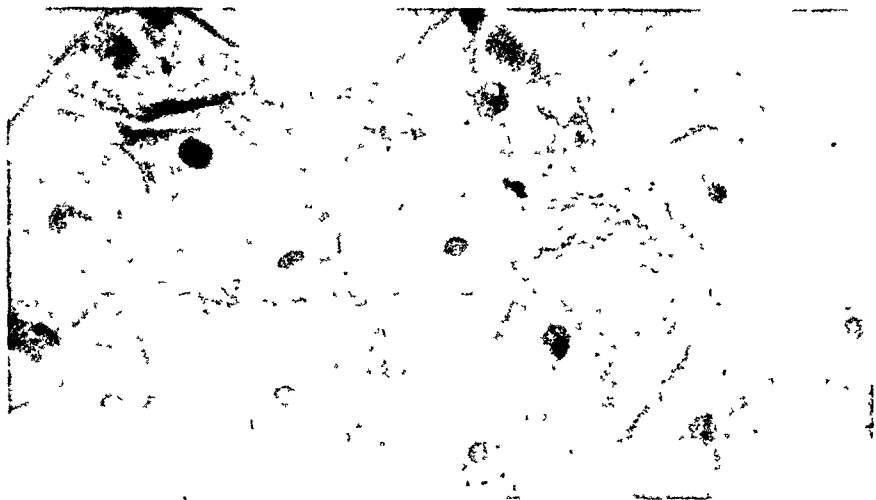


Fig. 8.—Most of the cells are cornified and there is no mucoid substance in this smear.

TABLE II. ADVANCED ESTROGENIC SMEARS IN RELATION TO THE FETAL SEX

STAGE OF PREGNANCY (WEEKS)	TYPE OF SMEAR	SEX PREDICTED	SEX DELIVERED
16	AE	Female	Female
19	AE	Female	Female
21	AE	Female	Female
21	AE	Female	Male*
23	AE	Female	Female
24	AE	Female	Female
24	AE	Female	Female

AE—Advanced estrogenic *—Error

Discussion

These data are in accordance with earlier findings in pregnancy.⁷ The cytolytic smear was found in women on estrogen therapy and in conditions with a high estrogenic level.⁶ Careful analysis of the smear itself shows evi-

*The six remaining women have since been delivered. There were three males and three females. Two errors occurred in respect to the cytolytic smear. This brings the relationship of specific smears to the fetal sex to an incidence of 81 per cent.

FACTORS INFLUENCING SUCCESSFUL POSTERIOR PITUITARY TREATMENT OF FUNCTIONAL UTERINE DYSTOCIA WITH PARTICULAR CONSIDERATION OF ITS INTRAVENOUS ADMINISTRATION

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THE problem presented by the functional failure of uterine contractions in labor, i.e., uterine inertia, remains unsolved. The recognition of this difficulty is not new, for as early as 1807 Stearns¹ had written of the use of ergot in "lingering labor." However, with the great strides made in recent years in the treatment of puerperal infection, obstetric hemorrhage and cephalopelvic dystocia, uterine inertia, through its defiance of therapy, has gained in relative importance.

Posterior pituitary extract has been available to stimulate uterine contractions since 1909. Even Blair Bell, who introduced it, recognized that it was not a safe drug in the first or second stages of labor. The chief danger in his day and the succeeding decade was due to unreliable standardization and to the use of huge doses. These two factors put the use of the drug before the birth of the infant in disrepute, and after 1920 many articles appeared decrying its administration in the first and second stages. Teachers of obstetrics either forbade its use entirely or advocated modified methods of administration, such as the intranasal route,² which gave uneven and unpredictable absorption. These teachings prevented adequate and controlled evaluation of the drug, although physicians away from the shadow of teaching centers continued to employ it in increasing numbers. Even with the modern well-standardized product the dosage was usually too large and frequently mere clinical evaluation of the pelvis missed the less obvious types of cephalopelvic disproportion. This led to unfortunate and, too often, tragic results which still further discouraged any real investigation of the true merits of pituitary extract in the treatment of functional dystocia. However, recently two careful pituitrin studies have appeared from major clinics. Both Reid³ and Eastman,⁴ although cautious in their conclusions, feel that the stimulation of contractions in cases of inertia with pituitary extract is an efficacious and meritorious procedure. Their figures show a definite and real decrease in the incidence of difficult vaginal deliveries in such cases. They have both emphasized the necessity of extremely small dosages, given intramuscularly, not more often than every thirty minutes. Both authors stress the contraindications which pelvic contraction, elderly primiparity, and great multiparity offer. It is obvious from the results of these studies that even in indicated cases pituitary extract will solve only a portion of the problems. Even Blair Bell was aware of this, for in 1938 Jeffcoate⁵ stated in the memorial lecture to his teacher that it was his cognizance of these occasional failures of pituitary stimulation that led him to urge the investigation of other drugs, such as estrogenic compounds in the treatment of uterine inertia.

Summary

The normal vaginal-smear changes during the course of pregnancy are presented. Increased cornification without mucification was encountered in only six cases. Three of these soon thereafter threatened to abort.

Specific estrogenic and androgenic smears are described and their significance and correlation to the fetal sex are discussed. The cytolytic smear consists of an increased number of Döderlein bacilli and complete destruction of cellular cytoplasm with intact nuclei and is believed to accompany high estrogen activity. This type of smear is associated with a female fetus. The mucoid cornified smear is the usual typical androgenic smear and is characterized by cornified cells with abundant mucoid material. The glycolytic type, with extracellular glycogen and intracellular glycopenia, is a very rare androgenic smear. Such smears are associated with a male fetus.

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Table II shows the distribution of cases by type of delivery and Tables III and IV by age and parity. These latter are definitely not factors influencing the outcome of this type of therapy. Most of the patients, but not all, were primiparas. Experience has taught that the treatment of highly parous or elderly individuals with antepartum pituitary stimulation is not wise. The only ruptured uterus in the series, reported in detail by Eastman, occurred in a 44-year-old para viii. Following this no pituitrin stimulation has been allowed in women of greater parity than iv.

TABLE II. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO TYPE OF DELIVERY

TYPE OF DELIVERY	SUCCESSFUL	UNSUCCESSFUL
Spontaneous	77	3
Low forceps, elective	102	3
Low forceps, indicated	151	12
Midforceps	0	3
Breech extraction	18	0
Willett forceps, successful	1*	2
Willett forceps, unsuccessful	3	1
Classical cesarean section	0	1
Low cervical cesarean section	0	5
Radical cesarean section	0	5
Extraperitoneal cesarean section	0	4
Twins	2	1
Low forceps, Dührssen incision	0	5
Midforceps, Dührssen incision	0	2
Total	354	47

*Pituitrin and Willett forceps begun simultaneously.

TABLE III. SUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION BY AGE AND PARITY

AGE	TOTAL	PARITY										
		0	i	ii	iii	iv	v	vi	vii	viii	ix	x+
< 20	61	56	5									
20-24	101	82	13	6								
25-29	85	64	15	4		2						
30-34	60	30	17	6	3	2	1				1	
35-39	38	18	8	4	2	2		1	1		2	
40+	9	2	1		1	1			1	2		1
Total	354	252	59	20	6	7	1	1	2	2	3	1

TABLE IV. UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION BY AGE AND PARITY

AGE	TOTAL	PARITY											UNKNOWN
		0	i	ii	iii	iv	v	vi	vii	viii	ix	x+	
< 20	10	9	1										
20-24	12	8	2	1	1								
25-29	8	7	1										
30-34	8	4	1		1				2				
35-39	5	4	1										
40+	4	1			1				1				1
Total	47	32	7	1	3				1	2			1

Tables V and VI deal with the time factor. Table V shows the distribution of cases according to successful and unsuccessful groups in relation to the duration of labor prior to the onset of treatment. In the analysis of these two groups the data were taken to be statistically different if the X^2 was 4 or

While the infant mortality figures of both Reid and Eastman are better than could have been achieved in such cases by any other present-day method of treatment, excluding of course the radical use of cesarean section, neither gave any special attention to those instances in which pituitary extract therapy failed. It is only when investigation is particularly directed toward this point that the poor quality of fetal results becomes apparent. With this in view, much of the same material reviewed by Eastman was re-examined and transferred to special punch cards.

Present Study

The following is an analysis of 488 cases treated with posterior pituitary extract during the first and second stages of labor from Jan. 1, 1941, to Dec. 31, 1945, at the Johns Hopkins Hospital. Both pituitrin and pitocin were used at various times and, while a slightly better response was elicited with the former, the difference was not statistically significant. In the following tables no attempt is made to differentiate between the two. From 1941 to 1943 the initial dose was limited to one minim intramuscularly, and thereafter to $\frac{1}{2}$ minim. Successive doses were never given more often than every thirty minutes, the injections sometimes being increased to 2 minims, depending upon the response. In no instance was a larger dose than 2 minims employed. All cases had clinically normal pelves, and in many this had been confirmed by x-ray pelvimetry. It is now mandatory in this clinic that the latter be taken prior to pituitary extract stimulation in every case to exclude unrecognized mid-pelvic contraction or asymmetry.

Table I groups the cases into successful, unsuccessful, and equivocal, in regard to the outcome of this specific type of therapy. These three terms are herein defined as follows: *Successful*—treatment with pituitary extract resulted in the full dilatation of the cervix and descent of the head to a level where an easy low forceps or spontaneous delivery was achieved. *Unsuccessful*—cases in which full dilatation of the cervix was not reached, or in which delivery had to be achieved by cesarean section or a difficult low or midforceps, or in which some other method of therapy in addition to pituitary extract was necessary. *Equivocal*—the use of pituitary extract in these cases was usually confined to one dose. Furthermore, in reviewing the cases, the essayist was not convinced

TABLE I. PITUITRIN STIMULATION. TOTAL FETAL MORTALITY IN INFANTS 1,000 GM. AND OVER DISTRIBUTED ACCORDING TO SUCCESSFUL, UNSUCCESSFUL AND EQUIVOCAL.

	DELIVERIES	DEATHS	MORTALITY	CORRECTED*	
				DEATHS	MORTALITY
Successful	354	16	4.5%	11	3.1%
Unsuccessful	47	10	21.2%	7	15.9%
Equivocal	87	2	2.3%	1	1.1 %

*Fetal heart not heard prior to pituitrin stimulation and congenital malformations incompatible with life omitted.

either by the length of the recorded delay in cervical dilatation or by the total length of labor that these were true cases of functional dystocia. The very low infant mortality rate in this group would seem to bear this out. The equivocal group will therefore be omitted from this analysis. The corrected and uncorrected fetal mortality in the various categories is also given in Table I. It is very striking that while the mortality rate in the successful group is close to the clinic average, there is a fivefold increase in the unsuccessful group.

For the past year all women in labor more than twenty-four hours have been given prophylactic penicillin. Prior to this and during the entire period of this study, such was not the case. Whether this has much influence on the occurrence of intrapartum fever remains to be seen. However, in the cases tabulated in Table IX, the occurrence during labor of an elevation of 100.4° F. by mouth or greater was a very important factor in determining the successful outcome of pituitary stimulation.

TABLE IX. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO INTRAPARTUM FEVER

	CASES	FEBRILE	AFEBRILE	PER CENT FEBRILE
Successful	354	46	308	12.99
Unsuccessful	47	15	32	31.91
$X^2 = 10.87$				

The clinical impression gained credence that cases of functional dystocia under pituitrin therapy did better with some form of pain relief. Various types of regional and general analgesia were tried but, as shown in Table X, the clinical impression remains unproved.

TABLE X. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO ANALGESIA

	CASES	ANALGESIA	NO ANALGESIA	PER CENT ANALGESIA
Successful	333	250	83	70.6
Unsuccessful	46	29	17	61.7
$X^2 = 3.59$				

In an effort to overcome certain very obvious objections to the intermittent method of pituitary extract stimulation, the use of highly dilute continuous intravenous therapy was resorted to. Pituitrin was mixed with either normal saline or 5 per cent glucose in concentrations of 0.5 minim per 50 cubic centimeter. This mixture is given intravenously at the rate of 50 c.c. for the first half hour and 100 c.c. per half hour thereafter. There was a very gradual and physiologic increase in uterine contractions which were maintained only so long as the solution continued to run, and ceased with the cessation of the treatment. Patterns of uterine contraction under this form of stimulation have been studied with the Reynolds tokodynamometer and will be reported in detail later. It is sufficient to say here that this appears to be a much more physiologic method of pituitrin uterine stimulation. Table XI is similar to Table I and shows the distribution of cases of functional dystocia treated by the continuous method. They are distributed according to the success of the therapy and the fetal mortality rates calculated. The failure rate is approximately the same with this technique as with the intermittent method. There were no infant deaths, but this is perhaps a sampling error due to the small number of labors treated.

TABLE XI. INTRAVENOUS PITUITRIN STIMULATION. TOTAL FETAL MORTALITY INFANTS 1,000 GRAMS AND OVER DISTRIBUTED ACCORDING TO SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION

	DELIVERIES	DEATHS	MORTALITY
Successful	36	0	0
Unsuccessful	7	0	0

greater. The X^2 being 7.72, any difference in percentage is significant. Thus a greater percentage of unsuccessful cases labored thirty hours or more prior to the onset of treatment than in the successful group. Similarly in Table VI a greater percentage of the successful group completed their entire labors in less than thirty hours.

TABLE V. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO LENGTH OF LABOR PRIOR TO FIRST DOSE OF PITUITRIN

	CASES	LABOR LESS THAN 30 HOURS	LABOR MORE THAN 30 HOURS	PER CENT LABOR LESS THAN 30 HOURS
Successful	354	299	55	84.46
Unsuccessful	47	32	15	68.09
$X^2 = 7.72$				

TABLE VI. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO THE TOTAL LENGTH OF LABOR

	CASES	LABOR LESS THAN 30 HOURS	LABOR 30 HOURS OR MORE	PER CENT LESS THAN 30 HOURS
Successful	354	266	88	75.14
Unsuccessful	47	19	28	59.57
$X^2 = 5.14$				

Table VII shows the station of the fetal head in both groups prior to the onset of therapy. This apparently was a factor of prime importance in the outcome of the therapy, for in 23.4 per cent of the unsuccessful cases the head was higher than two fingerbreadths above the spines, while in only 6.78 per cent of the successful cases was this true. This is, of course, a highly significant difference.

TABLE VII. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO THE STATION OF THE FETAL HEAD

	CASES	HEAD 2 FINGERS OR MORE ABOVE SPINES	HEAD LESS THAN 2 FINGERS ABOVE SPINES	PER CENT WITH HEAD 2 FINGERS OR MORE ABOVE SPINES
Successful	354	24	330	6.78
Unsuccessful	47	24	36	23.40
$X^2 = 14.39$				

In contrast to the station of the head, the dilatation of the cervix at the onset of therapy did not seem to play an essential role in the outcome, as shown by Table VIII.

TABLE VIII. SUCCESSFUL AND UNSUCCESSFUL PITUITRIN STIMULATION. DISTRIBUTION ACCORDING TO DILATATION OF THE CERVIX

	CASES	4 CM. OR MORE DILATED	LESS THAN 4 CM. DILATED	PER CENT 4 CM. OR MORE DILATED
Successful	354	265	89	74.86
Unsuccessful	47	30	17	63.83
$X^2 = 2.60$				

THE SIGNIFICANCE OF ABNORMAL MENOPAUSAL VAGINAL SMEARS

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NATIONWIDE publicity in the past year has brought many women to our Cancer Prevention and Detection Center for routine physical examination "check-up." Up to the present time, we have examined vaginal smears in approximately 900 women who had no specific complaints. Of these 42 per cent were within or beyond the menopausal age group. The smears in these patients fell into one of two types: the "crowded menopausal," seen chiefly in women at the onset of the menopausal syndrome; and the "atrophic menopausal," evident in women well within their menopause. Twelve out of a total of 378 cases, 3.16 per cent of these smears, presented a disturbing picture because of the marked resemblance that these particular smears bore to cases of proved cancer.

It has been apparent for some time that cancer cells grow for indeterminate periods before a tumor can be grossly recognized. True carcinoma of the cervix, particularly, can remain unnoticed for long periods of time notwithstanding regular pelvic examinations. On many occasions when cancer of the cervix is eventually recognized, careful review of previous biopsy specimens reveals previously unnoticed abnormalities.

Taylor and Guyer¹ recently reported a case in which a patient had been followed for a seven-year period for chronic cervicitis and cervical erosion, with repeated negative cervical biopsies. At the end of seven years, biopsy revealed a definite squamous-cell carcinoma of the cervix. When other sections were made of the original block of tissue, several slides showed small tongues of abnormal squamous cells extending into the fibrous stroma.

In 1945, Rubin² reported three early cervical carcinomas in three clinically unsuspected cases incidental to operations for plastic surgery.

TeLinde and Galvin³ also stress the fact that carcinoma of the cervix may be unrecognizable by clinical examination or even routine biopsy. Their finding of eight definitely cancerous lesions in normal or almost normal-looking cervixes in one year is rather startling. In none of these cases was a diagnosis of cancer possible from palpation or inspection of the cervix. In approximately half the cases, several well-trained gynecologic pathologists were unwilling to make a diagnosis of carcinoma from the changes noted in the biopsy specimens. In 90 per cent of the cases, the authors found, after removal of the cervix, absolute evidence of invasive carcinoma.

In all of the quoted references, no mention is made of routine vaginal smears. The smear technique has been criticized to a certain degree, because of the time involved in studying slides. It has been further claimed that the

Conclusions

1. In 401 cases of functional uterine dystocia treated with intermittent small intramuscular doses of pituitary extract, failure to achieve easy delivery occurred in 11.7 per cent.

2. Factors contributing to the failure of this form of therapy were: (a) long duration of labor; (b) long duration of labor prior to treatment; (c) intrapartum fever; (d) high station of head when treatment was first instituted.

3. Factors playing no part in the failure of this form of therapy were: (a) the extent of dilatation of the cervix at onset of therapy; (b) analgesia.

4. Continuous intravenous injection of posterior pituitary extract while apparently a more physiologic form of therapy, did not increase the success rate.

5. The excellent fetal results in both successful and unsuccessful groups of intravenously stimulated patients are encouraging, but might not be confirmed in a larger series.

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All of these instances of delayed cancer diagnosis indicate that carcinoma can exist without clinical signs and/or symptoms of malignancy, and is even unrecognizable by histologic study. The knowledge of the above has made us



Fig. 2.—Atrophic menopausal smear showing atypical cellular changes.

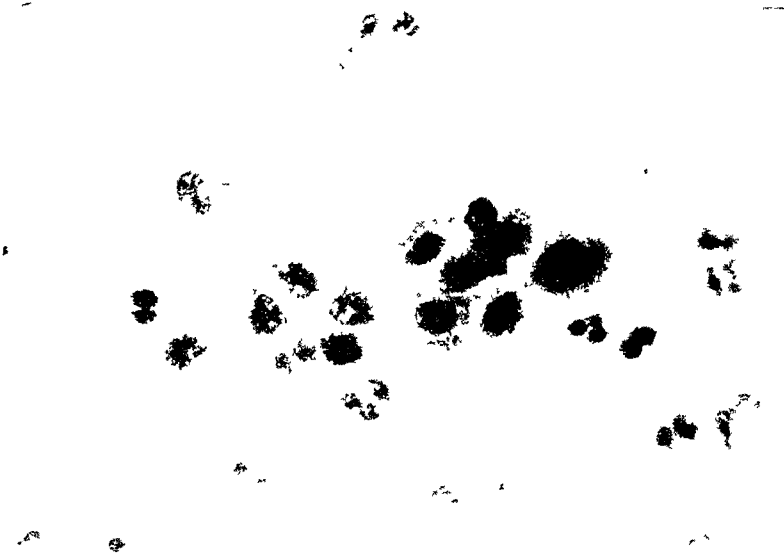


Fig. 3.—Cluster of basal cells from atrophic menopausal smear. Note the anisocytosis, anisonucleosis and nuclear hyperchromatism.

very wary in interpreting certain types of smears in our Center. Our uncertainty is particularly pointed in the case of certain types of menopausal smears.

examination of the slide is a tedious, lengthy procedure and it is very possible to miss an abnormal cluster of cells in the smear. In our experience, we have not found it too difficult to detect an abnormal slide. With a sound training in interpreting normal cytology, a glance at an abnormal smear strikes one immediately in many cases. In such instances, a minute and lengthy examination follows.

The outstanding error which would discredit the value of these smears or the value of this "screening" method as developed by Papanicolaou, would be to entrust this work to inadequately trained technicians. The average well-trained technician should be able to aid the pathologist or cytologist by sorting the slides, but no clinic can expect to train a technician for one or two months and then entrust that technician with making diagnoses. An already well-trained pathologist or cytologist must spend ample time learning first the characteristics of normal vaginal smears and their interpretation and then become thoroughly familiarized with the abnormal cells.

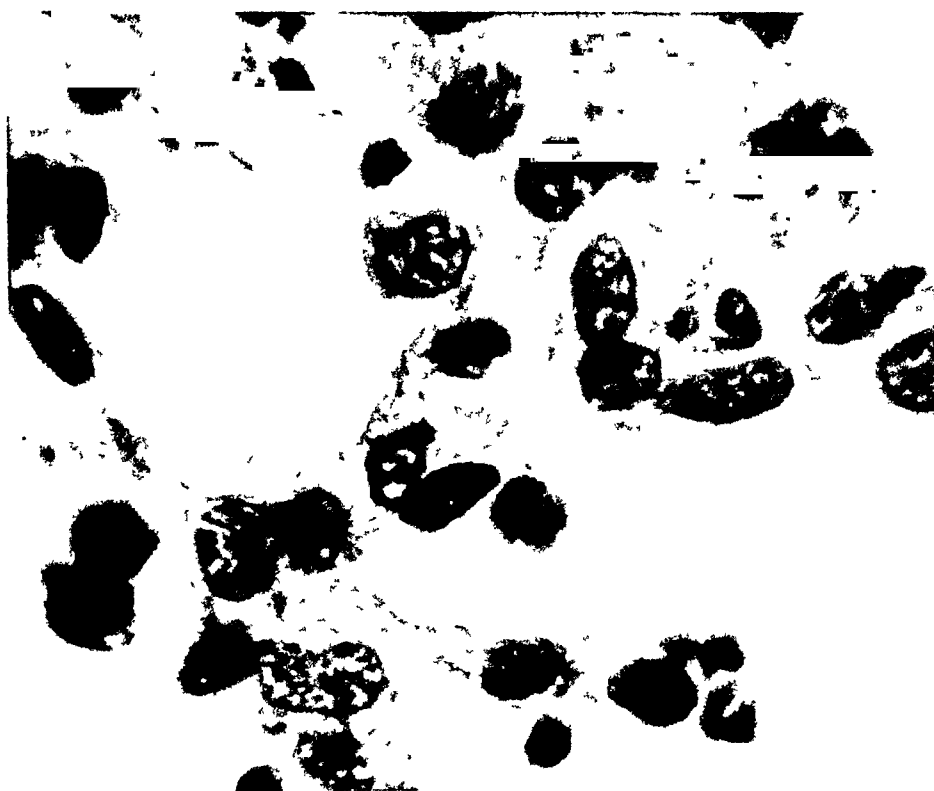


Fig. 1—Abnormal menopausal smear. Cells show variations in size, shape, staining reaction and density of the nuclear chromatin. These cells have some of the features of malignant cells but are non-cancerous. (Confirmed by repeated smears and multiple biopsies).

Perhaps examination of routine smears on these so-called normal-looking cervixes, described by TeLinde and Galvin, could have afforded some inkling of suspicion. The shedding exfoliative characteristics of genital tract malignancies are manifested prior to clinical signs or symptoms. Corroboration of the success and utility of this method has been amply provided by Papanicolaou and Traut,⁴ Meigs,⁵ Ayre,⁶ Jones, Neustaedter, and MacKenzie.⁷

of the cells. In some, vacuolization of the cytoplasm is clearly evident. The nuclei are bizarre in shape and in instances, hyperchromatic. Nucleoli are occasionally conspicuous. Elongation of the cells is a frequent occurrence. The cells sometimes become so long that they have lost their epithelioid form and acquire a close resemblance to smooth-muscle fibers. The most pronounced changes appear to be in the nuclei. They are relatively large, eccentric, indented, irregular in outline, bulge in all directions, and occasionally show hyperchromatism. Such cellular patterns ordinarily satisfy the criteria for malignancy in the vaginal smear.

Of all the 378 smears of menopausal patients examined at the Center, 3.16 per cent presented an abnormal pattern. Since our interest is primarily concerned with detection of early cancer prior to apparent clinical manifestations, we adopted the Papanicolaou classification of abnormal cells and malignancies in order to avoid missing very early cancer, and to study the significance of abnormal cytology, particularly in lieu of negative biopsy findings for malignancy. According to the Papanicolaou classification,* these can definitely be classified as Class III; they look very much like typical smears of carcinoma. Extensive studies in large series of cases by Papanicolaou reveal that 50 per cent of Class III smears are positive for malignancy. On the abnormal smears of menopause here discussed, biopsies have been repeatedly negative. These patients are being checked periodically by careful clinical examination, and smears are repeated every two to three months.

Are these cases of latent carcinoma? Are they potential malignancies for future diagnosis? Will repeated follow-up make a diagnosis of malignancy at a future date? Or are they just peculiar smears, seen during menopause? Are certain disturbances in hormonal equilibrium responsible for the peculiar picture? And if so, are they benign findings with no apparent significance? If the latter is true, the vaginal smear should be used with great discretion, and only by cytologists experienced in the diagnosis of cervical and fundal malignancy. This would eliminate a great number of false positives, unnecessary alarm, and unnecessary operative intervention in spite of negative biopsies.

Summary

1. We have shown that 3.16 per cent of all smears made in 378 menopausal patients present an abnormal pattern similar to that seen in carcinoma.
2. We believe that an intensive follow-up study is essential to evaluate the smear technique in the early detection of female genital cancer.
3. Leaving the interpretation of these smears to inadequately trained personnel will discredit the procedure.
4. Only a vast experience over a long period of time will prove whether or not these smears are merely misleadingly suspicious, or are really very early indications of a carcinoma which will be proved by standard and recognized methods at a much later date.

*Papanicolaou Classification:

- Class I. Absence of abnormal or atypical cells.
- Class II. Atypical cells present but without abnormal features.
- Class III. Cells with abnormal features but not sufficiently pathognomonic.
- Class IV. Fair number of pathognomonic cells and cell clusters.
- Class V. Large number of conclusive cells and cell clusters.

In examining the disturbing menopausal smears, repeated and numerous biopsies failed to reveal any definite evidence of carcinoma. In the photographs, the abnormal cytology is very apparent. The cells in the photographs

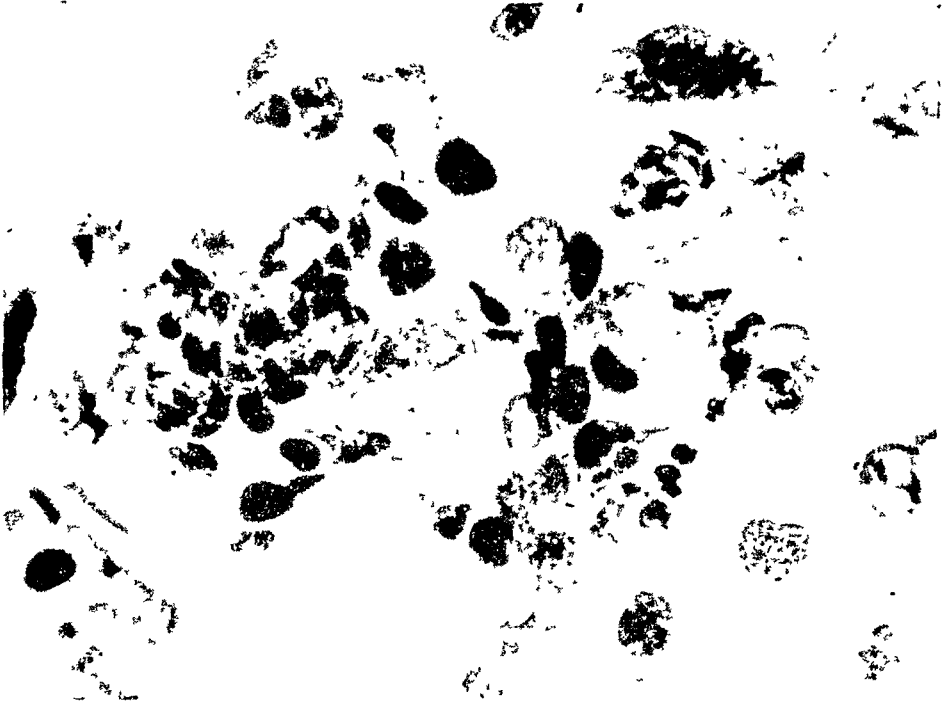


Fig. 4.—This smear is a proved case* of squamous-cell cancer of the cervix. Note the similarity in the cells in this smear and that of Fig. 1.

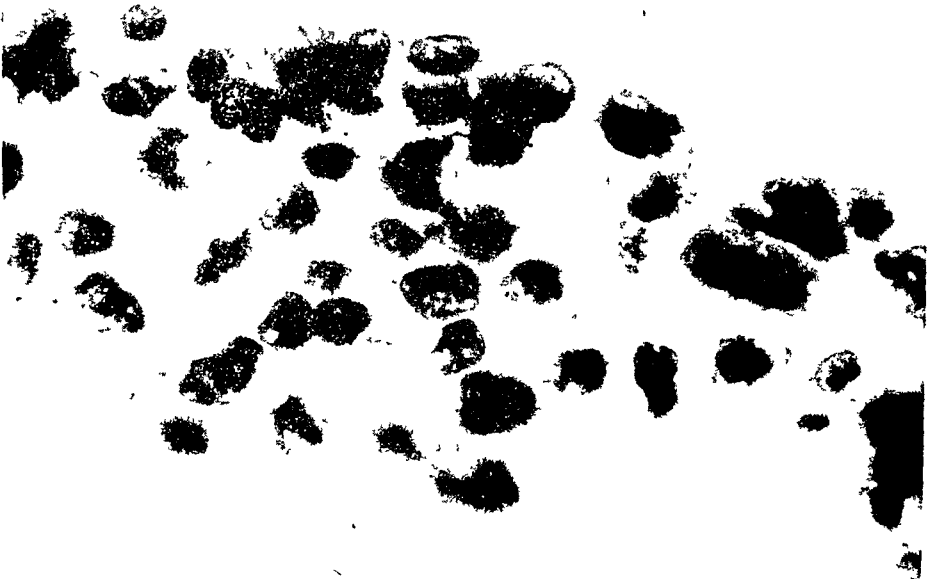


Fig. 5.—Squamous-cell cancer of the cervix.* Note the more marked anisonucleosis, anisocytosis, and nuclear hyperchromatism.

evidence a great variety of size and form. The cells in many instances tend to form dense groups with considerable overcrowding and overlapping. Some are relatively small and have comparatively large nuclei in relation to the size

*Confirmed by biopsy.

NONINVASIVE CERVICAL CARCINOMA

Clinical Features*

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PEMBERTON and Van S. Smith introduced the concept of noninvasive carcinoma or anaplasia of the cervical epithelium nineteen years ago, but pathologists in particular were unimpressed. Three years later Schiller of Vienna presented data on noninvasive cervical carcinoma before the New England Pathological Society.¹² Nevertheless, there is still not general acceptance of the idea that noninvasive anaplasia of the cervix is a malignant process. Anaplasia is defined to include collectively loss of cellular polarity and increased hyperchromaticity, hypertrophy, and variation in shape of the nucleus. Many believe these characteristics are sufficient to warrant a diagnosis of malignancy.^{1, 3, 4, 5, 7, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 24, 25} Whether or not the basement membrane is penetrated is immaterial to the fundamental nature of the epithelial growth, and merely determines the presence or absence of invasive qualities. Thus, penetration of the basement membrane is only a criterion of invasion and not of malignancy, while absence of it does not imply benignancy.

No one knows how long a noninvasive carcinoma remains localized before becoming invasive. Graves,⁹ as do others^{14, 24} estimate the time interval to be at least ten to twelve years. Most noninvasive lesions have been discovered by chance following incidental operation on the cervix. Recently, several were detected with cytologic methods.^{7, 15, 19} This report concerns seventeen women with noninvasive cervical carcinoma studied by cytologic methods and biopsy. Several of these were followed for a number of years.

Procedure

The diagnosis of noninvasive carcinoma of the cervix was seldom made at Parkland Hospital prior to 1946. Instead, it was usually reported as "anaplasia" or "hyperplasia." Cytologic methods instituted during 1946 for the detection of early cancer caused us to review all the records pertaining to hyperplasia and anaplasia of the cervix back to Dec. 31, 1935. Between that date and Jan. 1, 1946, ten specimens were found which on review were interpreted as noninvasive carcinoma. Seven other new cases were detected between Jan. 1, 1946, and Nov. 1, 1947.

The cervical smear and scraping or vaginal smear were used to study most of the patients. The vaginal smear was employed if the cervix was not present. Most of the women with a uterus had a cervical biopsy for serial sectioning and study, and then a total hysterectomy.

*Partially supported by the American Cancer Society, Texas Division, Inc.

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TABLE I. NONINVASIVE CERVICAL CARCINOMA

PATIENTS	AGE	APPEAR- ANCE OF CERVIX	DATE SEEN	PROCEDURE	HISTOLOGIC DIAGNOSIS	REMARKS	
1	38	Normal	July, 1938	Autopsy	Noninvasive carcinoma	Died of nephritis	
2	22	Eroded	4/13/39	Biopsy	Noninvasive carcinoma	Untraced	
3	29	Mild erosion	7/27/40	Subtotal hysterectomy and cauterization cervix	Noninvasive carcinoma	Untraced	
4	33	Eroded	4/25/41	Cervical biopsy	Noninvasive carcinoma		
	34	granular	6/26/42				
	36	Leucoplakia	12/20/44	Cervical scraping	Anaplastic epithelial cells		
	37	Eroded	11/ 5/45				
	39	Normal	8/24/47				
5	39	Eroded	8/25/47	Cervical biopsy	Noninvasive carcinoma	Followed 6½ yrs.	
			8/28/47	Hysterectomy	Noninvasive carcinoma		
			10/ 1/41	Subtotal hysterectomy and cauterization cervix	Noninvasive carcinoma		
	6	45	Normal	10/21/47	Cervical smear	Normal	Followed 6 yrs.
		47	Normal	8/25/41	Cervical biopsy	Cervicitis	
7	53	No data	Aug., 1947 7/ 9/43	Vaginal smear	Normal	Followed 6 yrs.	
				Cervical biopsy	Noninvasive carcinoma		
	55	Normal	4/15/47	Amputation cervix	Noninvasive carcinoma	Followed 3¼ yrs.	
8	24	No data	10/25/43	Cervical biopsy	Noninvasive carcinoma	Normal delivery	
	25	No data	7/25/44	Cervical smear	Normal		
	27	Normal	6/ 1/46				
	28	Normal	9/23/47				
			11/10/47		Cervical smear	Normal	Followed 4 yrs.
9	31	Eroded	8/ 8/44	Cervical biopsy	Noninvasive carcinoma		
	34	Normal	4/28/47	Cervical biopsy	Noninvasive carcinoma	Followed 2 yrs.	
10	22	Polyp	9/27/45				
	24		Sept., 1947			By letter found to be living and well	
11	37	Eroded	2/21/46	Cervical biopsy	Noninvasive carcinoma	Followed 17½ yrs.	
	38	Normal	8/31/46	Cervical smear	Anaplastic epithelial cells		
		Small erosion	9/25/47				
			10/ 7/47	Cervical biopsy	Noninvasive carcinoma		
			11/12/47	Cervical smear	Anaplastic epithelial cells		
		11/13/47	Total hysterectomy	Noninvasive carcinoma			

Incidence

A philosophy of cancer consciousness was introduced at Parkland Hospital with the formation of the present Department of Obstetrics and Gynecology in January, 1944. Eventually more careful pelvic examinations with visualization of the cervix were done and better records made. Previous to Jan. 1, 1944, subtotal hysterectomy was done. After that date total hysterectomy became the procedure of choice. Early in 1946 cervical and vaginal smears were employed in selected cases. Later in the year multiple, rather than single, samples were taken from tissues to be examined microscopically. Almost as many non-invasive carcinomas of the cervix were discovered in the last twenty months (seven cases) of the period of study as were found in the preceding ten years (ten cases). During this period of time, the clinic population remained relatively stable.

Age of Patient

The average age of patients with noninvasive carcinoma was 36.2 years, as contrasted to 43.5 years for women with frankly invasive carcinoma treated in the same clinic. One in three of those with noninvasive lesions was under 30 years old, while the corresponding figures for those with invasive cervical carcinoma were one in thirty-eight.

Signs and Symptoms

The usual signs of cervical carcinoma, as vaginal bleeding or leucorrhea, were seldom present. The cervixes of nearly one-third of the women with non-invasive lesions originally appeared normal, while those of the remaining number were "eroded," or the description was unavailable. Subsequently, one-third of the erosions disappeared. In other words, over one-half (ten) of the cervixes were grossly normal sometime during the period of observation. Seven patients had no symptoms referable to the genital tract between the time of the first biopsy and the follow-up study.

Results

Collected data for the 17 women with noninvasive carcinoma are given in Table I. For the purpose of discussion they are considered in three categories. The first included four patients untraced, died of causes other than cancer, refused complete examination, or contacted only by letter. The second group contained six patients seen nineteen months to six years after the original biopsy was taken. Two, treated by cervical amputation, were well six years later. Three still had noninvasive carcinoma, while the sixth showed no evidence of atypical cervical growth. The third group was composed of the seven women with noninvasive carcinoma seen during the last twenty-month period of this study.

In every instance where anaplastic epithelial cells were found in the cytologic smear, anaplasia of the cervical epithelium was noted in the biopsy.

Comment

The day has passed when anaplastic epithelium can be considered non-cancerous,⁴ or at the most only precancerous, because it is confined by the basement membrane. Apparently the life of a cervical cancer covers a period of many years during which there may be a long irritative stage of cervicitis and a shorter period of clinical latency.⁹ There are, at least, three reasons why some pathologists are loathe to agree that anaplasia without invasion is a form of cancer. First is the paucity of patients with noninvasive carcinoma followed until they developed invasive carcinoma. Reports of only fifteen such were

The average age of women with frankly invasive cervical carcinoma is 46 years.^{6, 11} On the other hand, the average age for noninvasive cervical carcinoma was 41 years, as determined by a combined analysis of 147 patients from our own material and that of others.^{11, 13, 14, 15, 18, 19, 20, 21, 23, 25} Pund and Auerbach,¹⁴ by studying consecutive cervical specimens examined in their clinic, found the average age was 36.6 years. The age differences indicate that it takes several years for cervical carcinoma to become recognizable clinically and that the noninvasive lesion is found relatively early in life compared to overt invasive carcinoma.

It would be interesting to know how early noninvasive carcinoma actually begins. From the standpoint of treatment, this fact is extremely important. Here, if ever, is the *ideal time to cure cancer*. Noninvasive carcinoma can be treated with a low operative mortality and few sequelae, while the treatment of frankly invasive carcinoma carries a high mortality from the disease alone and a comparatively high incidence of sequelae to treatment used.

Finally, we are of the opinion, as are others,^{2, 7, 19} that the cytologic smear is a valuable adjunct in detecting the presence or absence of noninvasive cervical carcinoma.

Summary

Of 17 women with noninvasive carcinoma, over a third were under 30 years old. Several of the patients had a normal appearing cervix and presented no symptoms referable to the genital tract. In two instances the carcinoma remained localized over six years. Cytologic methods were a reliable adjunct to biopsy in detecting the presence of the noninvasive cervical carcinoma.

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TABLE I—CONT'D

PATIENTS	AGE	APPEAR- ANCE OF CERVIX	DATE SEEN	PROCEDURE	HISTOLOGIC DIAGNOSIS	REMARKS
12	45	Erosion	3/30/46	Cervical biopsy	Noninvasive carcinoma	
			4/11/46	Total hysterectomy	Noninvasive carcinoma	
13	60	Normal	10/27/47	Vaginal smear	Normal	Followed 17½ yrs.
			4/ 1/47	Cervical smear	Anaplastic epithelial cells	
			6/ 6/47	Biopsy	Noninvasive carcinoma	Refused further treatment
14	37	Normal	4/15/47	Total hysterectomy	Noninvasive carcinoma	Chronic pelvic inflammatory disease
15	26	Eroded	July, 1947	Total hysterectomy	Noninvasive carcinoma	Chronic pelvic inflammatory disease
16	35	Normal	4/24/47	Total hysterectomy	Noninvasive carcinoma	Chronic pelvic Inflammatory disease
17	28	Granular	10/24/47	Cervical smear	Anaplastic epithelial cells	
			10/25/47	Biopsy	Noninvasive carcinoma	
			11/ 6/47	Hysterectomy	Noninvasive carcinoma	

found.^{8, 11, 16, 18, 20, 21, 23, 25} Apparently all these observations were made by hindsight. One of these women remained well for nearly twenty years, but ultimately developed clinically invasive carcinoma. Second, in a few instances, the patient remained healthy. Perhaps all of the anaplastic lesion was excised in the first biopsy, the patient died of some other disease before clinical cancer appeared, or the original histologic interpretation was incorrect. Finally, there are those who do not consider a lesion as cancer until invasive properties are demonstrable.²⁰ This is a matter of definition of the word "cancer." Such a position immediately and surely prevents study of early cancer by refusal to accept the possibility that cancer cells may have an infancy and an adolescence. It would appear desirable to define "cancer" according to cell morphology rather than the stage to which growth has progressed, since specific chemical and morphologic properties of malignant tumor cells are now known to exist and can be recognized. This attitude is essential if we ever hope to make the earliest recognition of cervical carcinoma.

Replacement of the epithelium in the cervical glands by downgrowth of anaplastic surface epithelium has been regarded by some observers as evidence of early invasion. But there is reason to believe that invasion of a gland does not have the same importance as frank penetration of the basement membrane. Patient 4 presented evidence of extension into the cervical glands over a six-year period illustrating these changes may remain latent for several years and behave as a malignancy limited to the surface. It is known that different types of fully established tumors have a different capacity to grow and destroy. Therefore, it is reasonable to assume that a developing cancer does not grow with the same momentum as does a fully established tumor.²²

June 24, 1946, showed no change, and it was not until July 24, 1946, after the patient had missed two periods, that the diagnosis of pregnancy could be established by examination. Probable estimated date of confinement Feb. 25, 1947.

Prenatal course was uneventful. Total weight gain was 12½ pounds. No blood pressure elevation, urine was negative throughout. X-ray pelvimetry on January 22 revealed a breech presentation left sacroanterior and the following measurements: inlet anteroposterior 9.75 cm., transverse 12.25 cm., interspinous 10 cm., outlet intertuberosus 9 cm., posterior sagittal 5.5 cm. In view of the presentation and small pelvis, cesarean section was thought advisable. On March 5, 1947, she was admitted to the hospital for elective section. On the same night, she fell into labor spontaneously, and section was performed after 3 hours. The male infant weighed 5¾ pounds and had good muscle tone. He breathed and cried spontaneously. About twelve hours after birth, he began to have respiratory distress with occasional apnea. Cyanosis was present, but not marked. Twenty-four hours after birth a systolic murmur was heard over the precordium. X-ray showed an enlarged heart. In spite of constant oxygen and other supportive measures, he died forty-eight hours after birth.

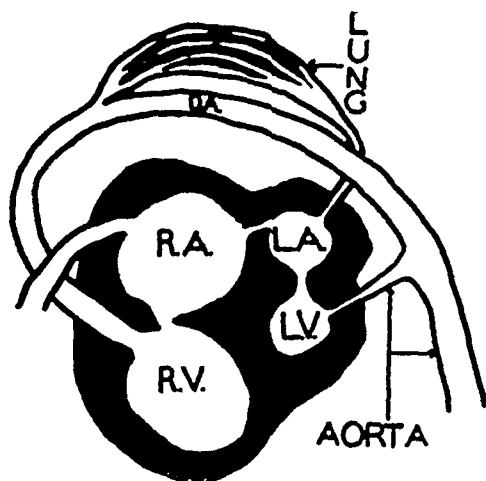


Fig. 1.—Diagram of heart, roughly representing the anatomical relations and relative size of the heart chambers and great vessels. R.A. = right auricle. R.V., L.A., and L.V. = succeeding chambers. D.A. = ductus arteriosus.

At post-mortem (Willimantic Autopsy No. 45), there was seen an externally normal male infant. A complete examination, excepting eyes, showed changes only in the heart and great vessels. The essential finding was a marked hypoplasia of the left auricle, left ventricle, and aorta in a 15 Gm. heart. Right chambers were relatively and absolutely hypertrophied, showing between 5 and 6 times the dimensions and capacity of those on the left (Fig. 1). Arrangement and sequence of great vessels, valves, and chambers were normal, as were their anatomical relations. Valve circumferences were, tricuspid 32 mm., pulmonic 23 mm., mitral 10 mm., and aortic 8 mm. The aorta was 3 mm. in diameter at the base of the heart and 5 mm. at its junction with the 6 mm. ductus arteriosus. The interventricular septum was intact, and the foramen ovale persisted as an oblique communication 1 mm. in diameter and 3 mm. in length. It was anatomically patent and functionally closed.

The endocardium of the left ventricle, and, to a less degree, that of the left auricle, showed a gray-white thickening which obliterated or flattened trabeculae and papillary muscles. In the structure first named, the process was 1 mm. thick in many sites, and obliterated the normal transparency of the endocardium. Microscopically, the process was one of fibrosis with varying degrees of cellularity and hyaline change (Fig. 2). Grossly and by section, this fibrotic change was characteristic of endocardial sclerosis.

We feel that there are two observations of significance in this heart. The first is that of severe and fatal congenital heart disease, assuming the form of hypoplasia of the left chambers and of the aorta. This deformity, often occurring with aortic stenosis or atresia,

INFECTIOUS MONONUCLEOSIS COMPLICATING PREGNANCY WITH FATAL CONGENITAL ANOMALY OF INFANT

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IN RECENT years, maternal rubella in the first trimester of pregnancy has been shown to be closely associated with high incidence of congenital anomalies in the offspring, and, at the present time, various other virus diseases are under suspicion. Infectious mononucleosis is generally considered a virus infection, although there is no conclusive evidence to support this contention. Its incidence in the general population is unknown because the diagnosis is frequently not made and because it is not usually a reportable disease. Therefore, we are reporting the coincidence of conception and infectious mononucleosis, with results disastrous for the fetus.

Mrs. R. K., a 27-year-old nulligravida, consulted one of the authors for the first time on May 20, 1946, complaining of vaginal discharge which had been present since the onset of the menses, and of general malaise for one month. Discharge was continuously present, rather thick, colorless, and odorless, and troubling her by causing chafing of the thighs. All sorts of douches had been tried without success. Catamenia began at 11 years of age, every 28 days, for four days. Several periods at fifteen-day intervals a few years previously had caused a physician to suspect miscarriage, but this was never confirmed. Last menstrual period May 14, 1946.

For the preceding month she had felt poorly, with arthralgia in fingers and knees, poor appetite, and restless sleep. For ten days prior to the first visit she had a daily afternoon chill, with temperature to 100.6° F. Since May 18, 1946 there had been mild sore throat. In the preceding week she had lost six pounds.

Past history, family history, and review of systems were essentially noncontributory.

Physical examination revealed a small woman, 4 feet 10 inches in height and weighing 116 pounds, who appeared tired but not particularly ill. Temperature 98.2° F., blood pressure 110/60. The only positive physical findings at this time were limited to the tonsils, which were both large, juicy, and rather dusky in appearance, with a small ulcer and many plugs of exudate on the right. The ulcer was covered by a gray adherent membrane. No lymph node enlargement was evident. Pelvic examination was completely negative.

Laboratory Findings.—Red blood count 4.89 millions, hemoglobin 14 Gm., white blood count 15,150. *Smear:* Polymorphonuclear leucocytes 22 (nonsegmented 14), lymphocytes 70, large mononuclears 6, questionable myelocytes 2. Many of the lymphocytes were suggestive of infectious mononucleosis. *Urine:* Yellow, acid, specific gravity 1.015; sugar, albumin, and sediment negative. Smear of tonsillar ulcer showed a few fusiform bacilli.

At this time, a diagnosis of either Vincent's angina or infectious mononucleosis was considered. It was believed that the vaginal discharge was not abnormal in amount or type but caused irritation because of plump thighs and profuse perspiration. She was given penicillin-beeswax, 300,000 units intramuscularly. The next day her throat looked worse and a second blood smear appeared typical of infectious mononucleosis, and blood taken at the previous visit was reported as showing a heterophile antibody titer of 1:640. Previously taken throat cultures and Mazzini flocculation were negative. She was followed during the next two months and gradually recovered. Meanwhile she failed to menstruate. Pelvic examination on

Summary and Conclusions

Recapitulation of the clinical history indicates the following chronologic sequence:

1. Onset of symptoms referable to infectious mononucleosis May 10, with vesperal fever, chills, and arthralgia.
2. Last menstrual period May 14.
3. Diagnosis of infectious mononucleosis established May 20 by positive heterophile test, blood smear, and clinical picture.
4. Presumed date of ovulation and conception based on known history of 28-day menstrual cycle, May 28.

It is clear, then, that this patient had active infectious mononucleosis at the time of conception and during the earliest stages of fetal development. She was observed through pregnancy and was delivered of an infant who promptly died of severe congenital heart disease.

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has been described by Abbott and others. It is the situation which Patten¹ describes as "the conspicuously defective development of the left side of the heart which is encountered when, as occasionally happens, abnormal development prematurely closes or markedly narrows the interatrial communication of the fetal heart."

The second observation to be emphasized is the subendocardial fibrosis involving the left auricle and ventricle. This finding is characteristic of endocardial sclerosis. In a recent review, Cosgrove and Kaump² have discussed the significance of this disease. They present data on 50 infants, of whom most had lived for a few days, occasional ones having survived for several months, and one child for five years. In all cases, the gross appearance of the heart was distorted to a degree compatible with a diagnosis of congenital heart disease.



Fig. 2.—Photomicrograph of section taken through thickened and fibrotic endocardium of left ventricle. A rather cellular fibrosis without inflammatory reaction, and a single large blood vessel are seen. At the bottom there is normal myocardium.

Microscopically, the lesions ranged from edema and degeneration through varying degrees of fibroelastic thickening and fibrosis of endocardium and myocardium. Thrombus formation, coronary vessel sclerosis, valvular verrucae, round-cell infiltrations, calcifications, and endocarditis were also observed. A controversy exists as to whether endocardial sclerosis represents a form of congenital heart disease caused by an inherent failure in the fertilized ovum or an infection transmitted from the mother. Although these authors have declared in favor of the first interpretation, we are inclined to feel that our case is better explained by infection. It is a heart whose fatal distortion shows no absence or serious displacement of structure, and which seems to be the result of a premature functional closure or stenosis of the foramen ovale. It also shows the characteristic lesion of endocardial sclerosis. We wish to present and emphasize co-incidence of these lesions with proved "infectious" disease in the early phases of this heart's development.

noted. No cells were found in the ascitic fluid and the nonprotein nitrogen in the ascitic fluid was 22 mg./100 c.c. During this time, 1,000 c.c. of 10 per cent and 1,000 c.c. of 20 per cent glucose were given. Adequate sedation was maintained with 100 mg. Demerol, 1/150 grain of scopolamine and 1½ grains of Seconal.

On April 30th, after eleven hours of interrupted labor, a viable female child weighing four pounds, fifteen ounces was delivered spontaneously. Urinary output since admission to hospital was 760 c.c. and the blood pressure ranged from 140/100 to 160/105.

On May 1, blood pressure was 140/100 to 170/122. Urinary output was 200 c.c. the first eight hours. Two hundred fifty cubic centimeters of two times concentrated plasma were given on two occasions at twelve-hour intervals. During this time, 1,000 c.c. of 5 per cent and 1,000 c.c. of 10 per cent glucose were given. Urinary output for the twenty-four-hour period increased to 4,700 c.c. Laboratory data: urine, 3.5 per cent moist albumin, serum protein, 4.52; bromsulfalein: Control 0 per cent, five minutes 70 per cent, and thirty minutes 25 per cent.

On May 2, blood pressure was 138/76. Urinary output was 5,000 c.c., residual ascitic fluid seemed to be diminishing. Liver was smooth and not tender and could be palpated 4 to 5 cm. below the costal margin. Choline, 1 Gm., and methionine, ½ Gm., ordered three times daily. Laboratory data: urine, 2.5 per cent moist albumin, few hyaline and finely granular casts; serum protein, 4.69; albumin, 2.37; globulin 2.32, cephalin flocculation, one plus.

On May 3, blood pressure was 160/110. Urinary output was 3,400 c.c. Laboratory data: serum protein, 4.63; serum bilirubin, per cent promptness in direct reaction, 100 per cent; cephalin flocculation, negative; bromsulfalein; control 0 per cent, five minutes 30 per cent, and thirty minutes 0 per cent.

Phenolsulfonphthalein test, first hour 60 per cent (300 c.c.), second hour 5 per cent (200 c.c.); Fishberg concentration test, 1.015, 1.017, and 1.017.

On May 6, ascites could not be detected and patient has no complaints. Electrocardiogram was within normal limits and x-ray of chest was reported negative. Patient was discharged for further care at home.

On June 13, blood pressure was 134/100. Urine showed a trace of albumin with an occasional finely granular cast. The liver was smooth, not tender, and could be felt just below the costal margin.

October 22, blood pressure was 130/80. Complained of occasional headache and nocturia (one time). Liver could still be palpated. Urine, specific gravity 1.021, albumin, very faint trace, and microscopic examination negative.

Summary

A case of acute ascites in pregnancy is presented. There is little doubt that this is a true eclamptogenic toxemia of pregnancy. The course prior to this pregnancy and for the first thirty weeks gave no indication of any hypertensive state, albuminuria, or any unusual weight gain. The cause for the ascites can possibly be explained by one or more of the following: (1) low serum protein with alteration in the albumin-globulin ratio; (2) portal block (liver damage demonstrated by comparison of liver function tests taken immediately prior to delivery and five days post partum); (3) hemoconcentration, which is demonstrated by red blood cell counts and hemoglobin measurement taken at the same time as liver function tests, possibly enhanced a portal block by retarding the portal circulation.

The fact that this patient was an eclamptic with her first pregnancy must be kept in mind as the liver may have been sufficiently damaged at that time to reduce the liver reserve to a point where the added load of pregnancy could not be tolerated. This could have been the factor predisposing this patient to another severe toxemia associated with ascites. Liver biopsy was contemplated but not done.

ASCITES IN PREGNANCY*

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ASCITES associated with pregnancy is an infrequent finding. Modern textbooks make no mention of the condition, whereas textbooks of the nineteenth century give the subject some attention.^{1, 2} In a review of the records at Charity Hospital for the last ten years, only one case could be found in 55,000 pregnancies. This patient would probably have had ascites without pregnancy as she had a decompensated syphilitic heart lesion. As far as can be ascertained, pregnancy and ascites are mentioned in the literature thirty-eight times. Of these references, only eleven are in English, in which sixteen cases are reported. The first was recorded in 1791 and the last in 1887.³⁻¹³

Case Report

Mrs. K. J., Z-5103, aged 25 years, gravida iii, para ii, was admitted to Touro Infirmary at 5:15 P.M. on April 29, 1947.

Past History.—Patient had eclampsia in 1941 and was delivered of a normal male child. The patient's condition at that time was regarded as critical due to a very low urinary output associated with other findings of a severe toxemia. (High fever, rapid pulse and respirations, and high blood pressure.)

Present Illness.—The expected date of confinement for the present pregnancy was June 2. Physical examination and serology were negative. The pregnancy progressed normally until the thirtieth week, at which time a trace of albumin was found in the urine and the blood pressure was 124/90. There was a seven-pound weight gain in five weeks. Slight pretibial edema was noted. At this time she was placed on the following regime: bed rest, salt-free high-protein diet, fluids, ammonium chloride, sedation, and recording of weight and intake and output. The blood pressure was taken daily. Her condition remained satisfactory; her urinary output remained adequate but the albumin increased to three plus. No increase in peripheral edema was noted.

On April 29, with blood pressure of 132/90, a weight gain of three pounds in twenty-four hours was noted. The abdomen was considerably larger and a fluid wave was elicited. The gravid uterus could be balloted. She was advised to enter hospital. Efforts were made to evaluate her condition, having in view the possibility of evacuating the uterus as soon as circumstances would permit.

Laboratory data on Admission.—Red blood count 5,360,000, hemoglobin 15.8 Gm., white blood count 14,800 (polymorphonuclear leucocytes 57 per cent, basophiles 1 per cent, and lymphocytes 42 per cent), serum protein 4.32, nonprotein nitrogen 35 mg./100 c.c.

Three hours and fifteen minutes after admission she was found to be in labor; the abdomen was considerably larger and more tense. Labor progressed normally for a little over two hours when it suddenly ceased. At this time patient complained of nausea, vomiting, and inability to swallow. Examination revealed the cervix 6 cm. dilated and 80 per cent effaced. The membranes were ruptured, removing as much fluid as possible, but no further contractions were initiated. Due to great discomfort, a paracentesis was decided upon. Two thousand seven hundred fifty cubic centimeters of clear colorless fluid were removed, after which the patient was able to swallow, ceased vomiting, and uterine contractions were again

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PRECOCIOUS PUBERTY IN GIRLS

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THE constitutional type of precocious puberty is the most common type.¹ Cases in which the precocity is due to an ovarian tumor are less frequent, and the ovarian neoplasm in such cases is almost always a granulosa cell tumor. In reviewing the literature I find only two cases in which what appeared to be a simple cyst of the ovary was thought to account for the precocity. One was a case reported by Lull,² in which the lesion seemed to be a simple follicular cyst; the other case was reported by Mengert,³ who stated that the ovarian lesion may have been a follicular cyst. In the case now reported below, a simple cyst of the ovary was present.

Case Report

H. W., a Negro girl, was born on Jan. 8, 1931⁴ at full term with a normal delivery. She was thought to weigh 7 pounds at birth, was breast fed, walked at 9 months, and talked at 18 months. Dentition occurred at 6 months. She had measles at 2 years, pertussis at 4 years, varicella at 5 years, and mumps at 6 years. There were four siblings.

On May 26, 1937, when she was 6 years, 4 months old, she had vaginal bleeding for the first time. Three months before that she had had a vaginal discharge. Two months before the bleeding, swelling of the breasts had been noted. The first episode of bleeding lasted four days. Bleeding subsequently recurred every twenty-eight days, continuing to last four days each time, and was never very free. However, for three months before admission to the hospital she bled continuously.

Because of the bleeding she was admitted to the hospital on Aug. 29, 1938. At that time she was 7 years, 7 months old. She was well nourished, appeared in good health, and was large for her age. The breasts were precociously developed, and hair was present on the mons pubis. There was a slight bloody discharge from the introitus. This orifice was virginal. Rectal examination revealed an abnormal pelvis mass. An x-ray of the skull was normal. The sella turcica measured 11 mm. in length and 8 mm. in height. Blood counts and urinalysis were normal. The Wassermann reaction was negative. The blood pressure was 100/50. The weight was 76 pounds, temperature 98.6° F., pulse 110, and respirations 22.

A preoperative diagnosis of precocious puberty, probably due to a granulosa cell tumor of the ovary, was made. She was operated upon on Sept. 6, 1938. An ovarian cyst replaced the right ovary. It was thin-walled, filled with thin fluid, and measured 10 cm. in diameter. A right salpingo-oophorectomy was done. The appendix and a small left parovarian cyst were also removed. The tubes, uterus, and left ovary were recorded as being small. The right tube measured 7 by 0.4 cm. The pathologist reported a corpus luteum cyst (Figs. 1 and 2). The patient's convalescence was uneventful.

The follow-up was as follows: May 23, 1940 (aged 9 years): There was no bleeding since the operation. There were no complaints. A keloid of the scar was present. The hymen was intact. A normal infantile uterus was felt on rectal examination. The breasts were larger than normal for her age, and pubic hair was present, but the development of both was less than prior to operation.

Feb. 17, 1944 (aged 13 years): Amenorrhea persisted until the age of 12 when menstruation occurred. She menstruated regularly every month since then, flowing five days. Moderate dysmenorrhea occurred. The introitus was virginal. No abnormalities were found on rectal examination.

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had a form of precocious puberty due to the ovarian cyst. However, as this interpretation did not seem entirely satisfactory, Dr. Emil Novak was requested to give his views on the case. He reports⁵ his belief that the ovarian condition was a cystic, but normally functioning, corpus luteum, and that the case is one of the constitutional type. He suggests that the subsequent amenorrhea was of the functional type which is seen not infrequently in normal girls in the pubertal or adolescent stage.

Thus is reported a case of sexual precocity associated with an ovarian cyst, but possibly of the constitutional type. It may be that Mengert's and Lull's were similar to this case.

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1200 EAST BROAD STREET

Hellman, L. M., and Vosburgh, G. R.: Role of Transfusion in the Etiology of Erythroblastosis, J. A. M. A. 136: 79, 1948.

The authors wish to re-emphasize the fact that Rh compatibility should be determined for all women prior to transfusion and only Rh negative blood should be used in negative cases. They report cases of nine Rh-negative women who gave histories of previous blood transfusions and, as a result of the transfusions, the subsequent childbearing careers of these patients were gravely jeopardized. These nine women had had five normal children prior to their transfusions but had only two normal infants thereafter. Both of these normal children born after transfusion were Rh-negative, these women having heterozygous husbands.

WILLIAM BERMAN.

Aldrich, C. Anderson: The Advisability of Breast Feeding, J. A. M. A. 135: 915, 1947.

Human milk still remains the best type of milk for young infants, although it probably is not always a complete food after the first few weeks. Breast milk has a definite preventive and therapeutic value. It is the safest milk for premature babies who are mature enough to suckle at the breast.

As a technique, breast feeding is probably the best method of providing gratification and a sense of security to the babies. But even in artificial feeding the mother can impart an adequate amount of that security in her manner of handling the infant.

Contraindications include pathologic conditions in the breast or nipple and some disease processes in the mother. Minor objections to breast feeding can best be met during the antepartum care of the patient.

WILLIAM BERMAN.

July 21, 1947 (aged 16½ years): The last menstrual period was April 6, 1947. Weight 116½ pounds, height 60 inches, blood pressure 116/80. The uterus was soft and the size of a ten to twelve weeks' pregnancy.

On Dec. 30, 1947, this patient, lacking nine days of being 17 years old, entered St. Philip Hospital on the obstetrical service and was delivered at term on that day of her first child. She was discharged from the hospital on Jan. 6, 1948.

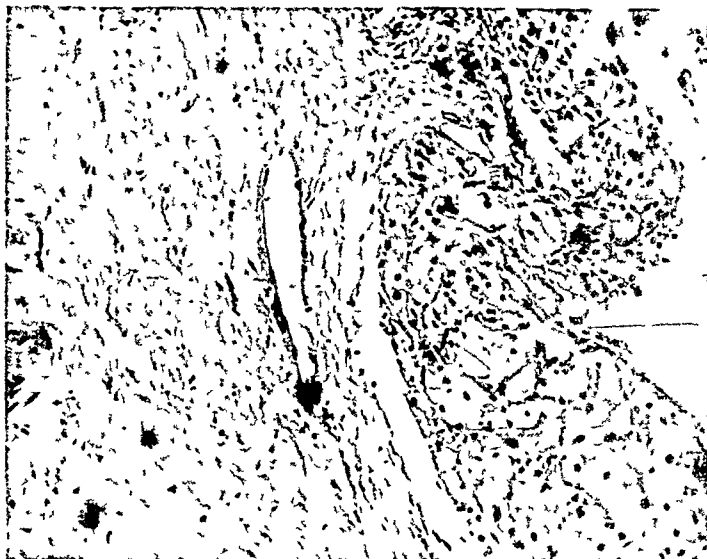


Fig. 1.—Section of ovarian cyst in a case of precocious puberty.



Fig. 2.—Precocious puberty. Section uterine tube, adult type.

Comments

The precocious puberty in this case was obviously not due to a *granulosa cell tumor*, suspected preoperatively, nor was any true tumor of the ovary found. Nevertheless, considering that a cyst with a diameter of 10 cm. replaced the right ovary and that there was some regression of secondary sex characteristics postoperatively, it was regarded that this patient

operation, a marked perinephritis was noted. The renal pelvis and upper ureter were found to be extremely dilated. An incision was made into the posterior surface of the renal pelvis, followed by a gush of purulent urine. A clamp was passed through the renal pelvis to the renal cortex. An incision was now made over the clamp and a No. 24 F. Pezzer catheter was drawn into the pelvis of the kidney. A cigarette drain was placed in the renal pelvis and the wound closed in layers. Following this procedure the temperature dropped to 99° F. and remained normal. The general condition of the patient definitely improved. At this point it was decided to explore the lower left ureter with the object of transplanting the ureter into the sigmoid. The patient was placed on a low residue diet. Sulfasuxidine was given by mouth. The patient was given daily enemas and two blood transfusions. On September 9,



Fig. 1.



Fig. 2.

Fig. 1.—Retrograde pyelography reveals a fairly normal left kidney. There is no evidence of ureteral obstruction.

Fig. 2.—Intravenous pyelogram taken five months later reveals a nonfunctioning left kidney.

under spinal anesthesia, a left rectus incision was made and the peritoneum opened. Numerous adhesions were encountered; these were separated. There was distinct infiltration of the peritoneum on the left side. The posterior peritoneum was incised at the level of the bifurcation of the iliac vessels, where the ureter was easily isolated. A large periureteral lymph node was palpated and easily removed. The ureter itself was thickened to the diameter of a lead pencil, and could easily be freed to a point about 3 cm. from the bladder. Below this, the ureter was normal in appearance. The ureter was clamped at this point and cut. The distal part was then ligated. The proximal part of the ureter was then brought up for a distance of about two inches and it was found to be completely replaced by solid tumor formation. The tumor-containing portion of the ureter was excised. Above this point the ureter was only moderately dilated, not enough to decide against transplanting it into the

METASTATIC CARCINOMA OF THE URETER IN CARCINOMA OF THE CERVIX

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IN 1933, we reviewed 50 cases of ureteral obstruction occurring in carcinoma of the cervix at the Brooklyn Cancer Institute. We have reviewed the cases which have entered the Institute since that time and the case herein reported is the only one in which either at autopsy or operation metastasis to the ureter was discovered.

Case Report

Case No. 33674, L. R., was admitted to the Brooklyn Cancer Institute on July 7, 1947, with a diagnosis of epidermoid carcinoma of the cervix, Grade III. The patient was a white woman, 40 years of age. She complained of pain in the lower back, radiating to the left leg. Extreme frequency and dysuria were present. When she was admitted, her temperature was 103° F., pulse 110, respirations 28. Extreme weakness and loss of weight were present. The patient had had two previous admissions to the hospital in 1947. All in all, she had received 9,000 mg. hr. of radium, divided into two doses, and administered by uterine tandem with colpostat and cork. Between Nov. 15, 1946, and Feb. 3, 1947, she had been given 6,660 r. units of deep x-ray therapy. On Feb. 21, 1947, urologic examination revealed a normal bladder mucosa. Both ureteral orifices were normal and both ureters could be catheterized without difficulty. Indigo-carmin injected intravenously returned in four minutes from both sides in good concentration. X-ray of the urinary tract and bilateral pyelography were negative. It was noted that there was a bifid renal pelvis on the right side. Following completion of the deep x-ray therapy, the patient was discharged from the hospital on June 1, 1947. She was readmitted on July 7 with the complaints previously noted. The left kidney was enlarged and tender and extreme lumbar spasticity was present. Pelvic examination disclosed the vaginal vault to be definitely contracted. The vaginal mucous membrane was pale; no ulcerations were found. The cervix was not palpable. On rectal examination, a mass the size of an orange could be palpated in the left parametrium. The urine was alkaline in reaction with a specific gravity of 1.024. Microscopic examination revealed innumerable pus and blood cells. Blood count showed a hemoglobin of 14 Gm., 4,700,000 red blood cells and 13,200 white blood cells, with polymorphonuclear leucocytes of 92 per cent and lymphocytes of 8 per cent. The blood urea was 11.5 mg., creatinine 1.2 mg., sugar 130 mg.

On July 9, two days subsequent to the patient's present admission, urologic examination disclosed evidence of a subacute cystitis. The right ureteral orifice was normal. Extreme bullous edema was noted at the left ureteral orifice. The ureteral catheter was obstructed on this side, at a point 2 cm. from the vesical orifice, and the obstruction could not be overcome. The right ureter could be catheterized without difficulty. Indigo-carmin injected intravenously returned in three minutes from the right ureter in good concentration. There was no return of the dye from the left side.

Intravenous urography at this time revealed a large, nonfunctioning kidney on the left side. The right pyelogram was normal.

The temperature remained elevated in spite of the administration of sulfonamide therapy and large doses of penicillin. Pain and tenderness in the left renal area persisted and a diagnosis of ureteral obstruction, with secondary pyonephrosis, was made. A left nephrostomy was decided upon. On Aug. 8, 1947, the kidney was explored under spinal anesthesia. At

bowel, especially since the nephrostomy tube was to be left functioning. The posterior peritoneum was then closed with No. 00 chromic catgut sutures. The sigmoid could be easily mobilized and the ureter was transplanted into the bowel by the technique of Coffey. The sigmoid was then fixed to the posterior peritoneum by means of two interrupted sutures of No. 00 chromic catgut. A cigarette drain was inserted into the abdomen and the wound was closed in layers.

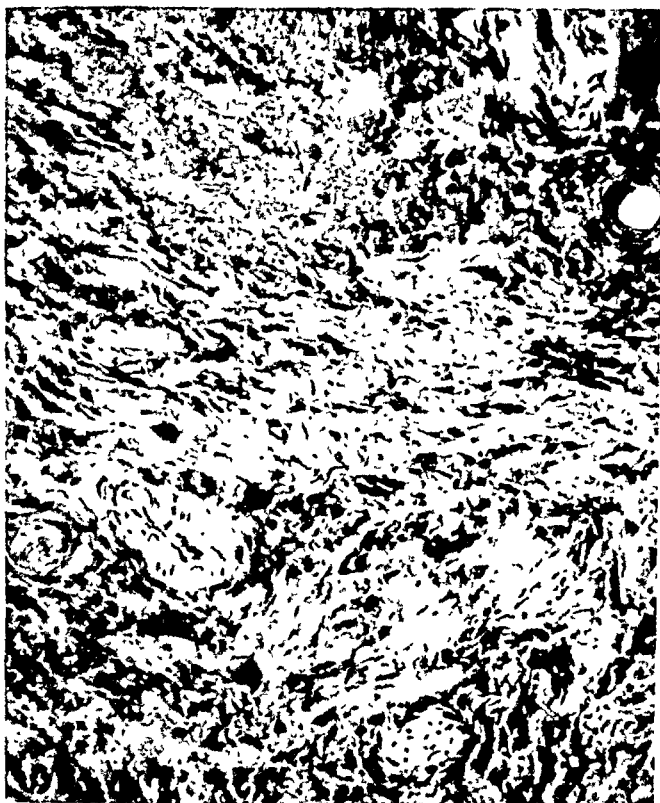


Fig. 5.—Section through periureteral lymph node showing complete replacement by tumor and fibrous tissue. ($\times 210$)

Pathologic Report (Dr. Herman Balkar).—Left ureter: Section through the ureteral wall shows marked widening and replacement of the muscular layer by fibrous tissue. There is no recognizable mucosa. All the layers are widely invaded by nests of atypical cells of the squamous-cell type. The nuclei are hyperchromatic and show marked variation in size and shape. Large areas are necrotic.

Diagnosis.—Metastatic squamous-cell carcinoma to the ureter of uterine cervical origin. Section of a periureteral lymph node shows complete replacement of lymphoid structure by sheets of metastatic squamous cells.

There was very little postoperative reaction. On the tenth postoperative day the nephrostomy tube was clamped. Passage of urine through the rectum was noted almost immediately. At this time the nephrostomy tube was removed. The patient was out of bed and up and about the ward, apparently doing well. On Oct. 21, the twenty-fifth postoperative day, the temperature rose to 104° F. The patient complained of pain in the chest and was extremely dyspneic. An x-ray of the chest taken the following day revealed the presence of a bronchial pneumonia associated with partial atelectasis of the left lung. With this the urinary output began to decrease and blood chemistry on October 26 disclosed 100 mg. of urea nitrogen. Intravenous glucose, penicillin, and then streptomycin were given. However, the patient appeared toxic and the temperature continued to run a septic course. She expired on November 15. Autopsy could not be obtained.

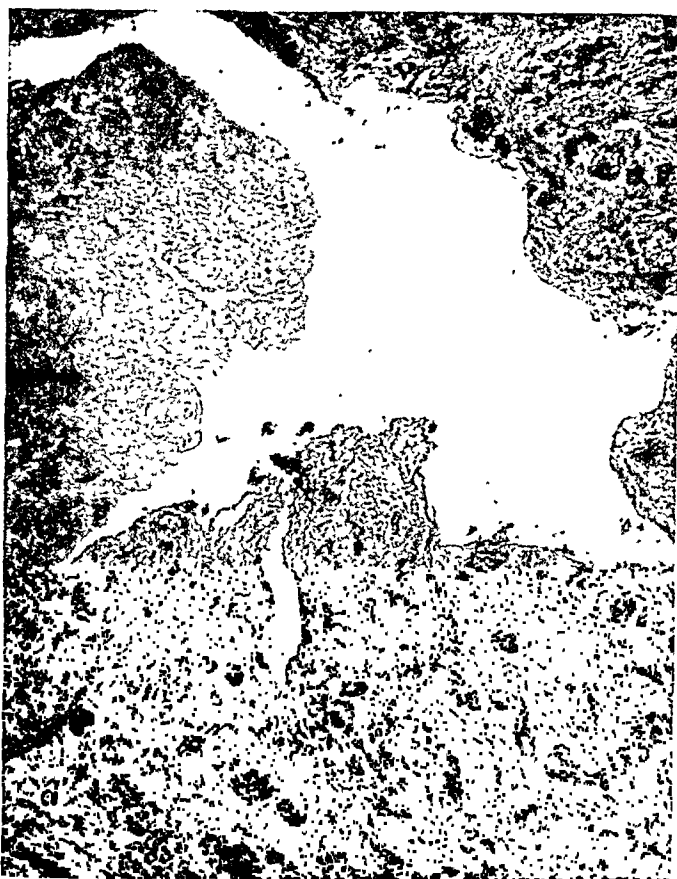


Fig. 3.—Ureteral wall showing destruction of mucosa and lymphatic invasion by nests of tumor cells. ($\times 50$)

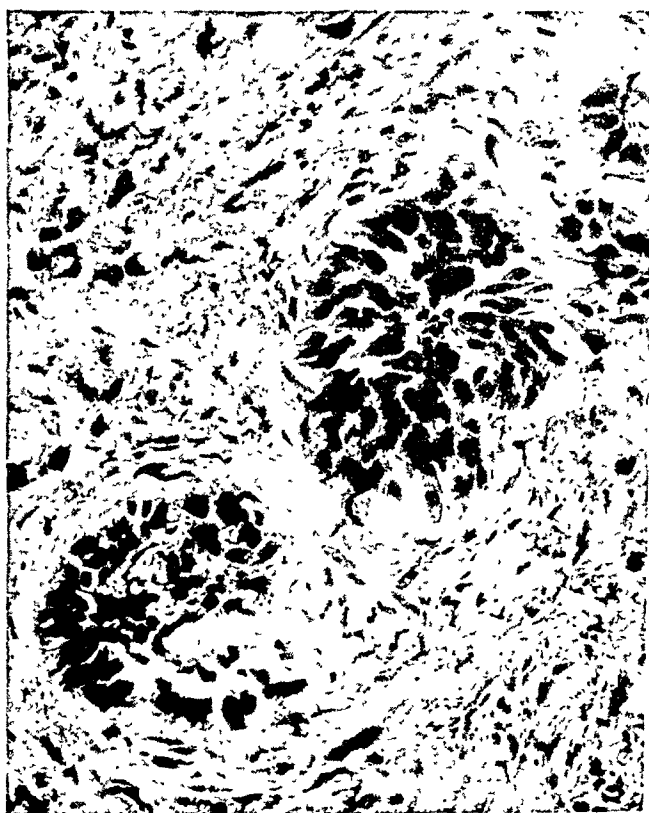


Fig. 4.—Nests of tumor cells in ureteral wall, marked desmoplastic reaction. ($\times 425$)

VAGINAL CARCINOMA IN A GIRL 14 YEARS OF AGE TREATED BY RADIATION

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SINCE primary carcinoma of the vaginal wall is relatively rare, it is not surprising that hardly half a dozen instances have been reported in patients 20 years of age or under. Moreover, too few of these reports^{1, 2} are recent enough and in sufficient detail for use as a guide in treatment. It is true there are to be found in the literature a limited number of individual case records concerning women of more advanced age, and also a few small series of primary vaginal carcinoma.³⁻⁹ In the latter the results almost without exception have been poor, though here, as in other malignancies of the female generative organs, a most important factor appears to have been delay in seeking advice. Even in early or relatively early cases, however, the low survival rates have failed to demonstrate definitely an efficient method of treatment, and surgical removal versus radiation is still considered debatable. Recently the argument seems to have been running in favor of radium plus deep x-ray therapy, particularly if the dosages can be made large, but much is yet to be learned before the situation can be considered satisfactory. Consequently, this case is of interest not only for its rarity, but also because it offers some additional data regarding therapy.

This girl was first seen on May 9, 1942, two weeks before her fourteenth birthday. Approximately regular vaginal bleeding, thought to be menstrual periods, had begun about eighteen months before. A few months before examination, however, bleeding had become almost continuous, though never profuse. Otherwise the history was unessential, as was also the examination except for the pelvic findings. The vagina admitted one finger, with which an irregular, soft mass was palpated in the upper part of the vagina. The possibility of a malignancy involving the cervix was suspected, and exposure by speculum permitted removal of a small piece of tissue. Microscopic sections from this showed advanced, medullary, squamous cell carcinoma.

On May 22, 1942, examination revealed a fungating growth about 3 cm. in diameter arising from the vaginal wall anteriorly and to the right, just below and not involving the cervix uteri. The elevated portion of the growth was curetted away, and 100 milligrams of radium in containers was tightly packed against the lesion. Examination of another piece of tissue confirmed the previous diagnosis. Radiation treatment was continued as described below:

First Series.—May 22, 1942. One hundred milligrams of radium in suitable containers, screened by 1 mm. brass and 1 mm. hard rubber were placed directly against the vaginal carcinoma, the surrounding structures being protected by a lead plate. The dose amounted to 3,600 milligram hours. From May 25 to May 28 supervoltage roentgen therapy was given externally through two portals, one anteriorly and one posteriorly, for the purpose of cross-firing the pelvis. A dose of 300 r in air was given alternately over each portal with an intensity of 20 r per minute at a distance of 60 cm. string target distance. Each portal measured 20 by 25 cm. The quality of the roentgen rays was that obtained with 500 kv. constant potential, 7 mm. Cu., 3 mm. Al., and 5 mm. celluloid. The total dose per portal thus amounted to 600 r in air. This was calculated so as to correspond, by including the percentage of transmission from the opposite portal, to a biologic dose of 100 per cent skin unit dose.

Summary and Conclusions

Although it has long been recognized that ureteral obstruction with secondary renal infection and uremia is the common cause of death in carcinoma of the cervix, there is considerable variance of opinion as to the mechanism of this obstructive process. It has been argued by many authors that fibrosis of the lower ureter follows radiation therapy in many instances. There is no doubt that fibrous tissue reaction does take place. However, this process of desmoplasia is a common reaction in carcinomatous invasion and it occurs with or without radiation therapy. The tumor spreads to the periureteral lymphatics and compresses the ureter. Involvement of the ureter itself is rare. Its occurrence suggests metastasis to the lymphatics within the ureter itself.

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Statistics show that in the State of Michigan the maternal death rate has been reduced from 10.47 in 1900 to 1.18 in 1946; and this improvement is nation-wide. This represents a significant scientific achievement. The use of the sulfonamides and, more recently, penicillin has resulted in the most marked decrease in infection as a cause of maternal deaths. But other factors are of importance in reducing maternal deaths, including the increasing use of blood transfusion, hospitalization for delivery, better understanding of the mechanism of labor, and improved prenatal care. There has also been a significant and striking decrease in infant mortality; in Michigan, the infant mortality rate in 1946 was one-fourth of that in 1900. While much of this decrease in mortality (in the first year of life) is credited to the pediatricians, the obstetricians are more directly responsible for the decrease in neonatal mortality. At present, prematurity is the chief factor in deaths in the neonatal period.

The increasing emphasis on prenatal care is one of the important factors in improving obstetric practice; it is a relatively recent development, the present standards for prenatal care having been developed in the last ten years. The great increase in hospital deliveries is also an important factor, as it is only in properly equipped hospitals that the risk from unforeseen complications of labor can be reduced. There are some disadvantages of hospital deliveries, such as, in some instances, unwarranted interference with the mechanism of labor, or overseparation of mother and child, with lowered incidence of breast feeding, but such disadvantages can be overcome. There is a tendency toward preventing undue prolongation of labor by the use of episiotomy and outlet forceps. While it may be found that these procedures are not always desirable, they have so far resulted in shortened labors, less exhausted mothers, and fewer maternal birth injuries. Early ambulation of obstetric patients has come back to obstetrics through the results of early ambulation in surgical operations, but the true value of this procedure cannot yet be established, probably not for another decade or two. However great the gains in obstetrics have been, there are many problems to be solved in the future.

HARVEY B. MATTHEWS.

INTRA- AND EXTRAUTERINE PREGNANCY

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IT IS the purpose of this paper to report a case of combined intrauterine and interstitial pregnancy in which the intrauterine pregnancy proceeded normally after resection of the cornu of the uterus, and eventuated in the delivery by cesarean section of a normal baby.

T. L., a 28-year-old Negro female, was admitted to the Charleston General Hospital, Jan. 30, 1947, with severe paraumbilical and right lower quadrant abdominal pains. Following the onset of her pains, she had been given a dose of castor oil by her mother and had vomited once. Shortly after the onset of the pain, she felt faint. There had been no definite shoulder pain. Her bowels had not moved since the day prior to admission, and there were no urinary complaints. There was no vaginal bleeding, and she did not think she was pregnant. She had had a normal four-day menstrual period beginning Nov. 18, 1946. On Dec. 18, 1946, she had had a scant two-day period. From Jan. 18 to Jan. 22, 1947, she had had an apparently normal period. She stated that two weeks before admission she had felt "poorly" and her family physician had made a diagnosis of pleurisy. One week before admission she had fallen down a flight of stairs injuring her back. Since then she had remained in bed most of the time. She had six children, the youngest being 6 months old. There had been no miscarriages, operations, nor serious illnesses. The family history was pertinent only in that her mother had had one set of twins.

Physical Examination.—The patient was a well-developed and well-nourished Negro woman with obvious abdominal distress and marked pallor of the mucous membranes. The temperature was 99° F., pulse 86, and the blood pressure 120/80. The abdomen was moderately distended. There was generalized abdominal tenderness with muscle guarding present over the lower abdomen, and marked rebound tenderness. There was no vaginal bleeding. The cervix was pale, firm, smooth, and closed. Because of marked tenderness on examination, the body of the uterus could not be well outlined. One examiner thought that there was a mass adjacent to the uterus in the right side of the lower part of the abdomen.

The hemoglobin was 49 per cent (Hayden), erythrocytes 2,500,000, leucocytes 15,000, with 82 per cent neutrophils and 18 per cent lymphocytes. Urinalysis showed no abnormalities.

A diagnosis of ruptured ectopic pregnancy was made, but the possibility of secondary hemorrhage from a ruptured spleen was also considered.

Blood transfusions were administered and operation was performed after the patient had received 750 c.c. of blood. The abdomen was entered through a subumbilical left paramedian incision. On opening the peritoneum a very large quantity of clots and fresh blood was encountered. The uterus was enlarged approximately to the size of a ten weeks' pregnancy, and was quite soft. Arising from a broad base at the right cornu of the uterus was an egg-shaped mass measuring approximately 6 by 5 by 4 centimeters. The right tube joined this mass anteriorly at its junction with the uterus. A narrow segment of omentum was attached to the apex of the mass, and beneath this there was active bleeding from a small perforation. The right tube was thickened and congested. There was a corpus luteum cyst in the right ovary.

The free blood and clots were removed. The attached omentum was doubly clamped, divided, and ligated. An assistant was able to control the bleeding by grasping the uterus proximal to the mass. The right tube was doubly clamped, divided, and ligated adjacent to

Second Series.—This consisted only of supervoltage roentgen therapy and was given from Aug. 14 to 18, 1942. The technique of procedure was identical to that used in the first series.

Third Series.—Only intravaginal radium was applied. On Oct. 15, 1942, 50 mg. of radium, in suitable containers, screened by 1 mm. brass and 1 mm. hard rubber, were placed opposite the site of the carcinoma for a total dosage of 1,800 milligram hours.

With the above treatment the tumor entirely disappeared about three months after the first two series. Two months later, however, it recurred as a small, pedunculated growth at the old site. This rapidly vanished following the second radium application, as described in the third series above.

The patient was last examined on Dec. 30, 1947, at which time there was no evidence of further recurrence. The introitus and vagina easily admitted one finger for about 6 cm., up to the site of the former growth. At that point the vaginal canal was contracted down to a size of about 5 millimeters. With a probe in this opening and the finger in the rectum it could be determined that the vagina above opened up again, and the small but normally situated cervix could be felt. The uterus was about one-third the usual size, and the adnexa were not palpable.

Of interest has been the approximately normal pubic and vulvar hair growth within a year or two after radiation. There has been rather little weight gain (from about 94 pounds to a maximum of 102 pounds), but the body contour has changed so as to resemble that of many women of her age. The breasts, however, are quite small, and there has been no suggestion of menstruation. Vaginal smears stained by the iodine vapor and the carbolfuchsin^{10, 11} techniques have shown a persistent and marked estrogenic deficiency reaction of the vaginal mucosal cells.

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955 FISHER BUILDING

In some of the cases of combined pregnancy, the uterus has been found enlarged at operation and has been removed. In others the uterus has been opened. This procedure could not conceivably do more than satisfy the surgeon's curiosity. Occasionally a dilatation and curettage have been performed prior to a celiotomy for ectopic pregnancy, and an intrauterine pregnancy thus unnecessarily aborted.³ Such mistakes may be avoided if one bears in mind the possibility of a combined pregnancy. In some cases, the intrauterine pregnancy will abort due to operative trauma, the influence of excessive intraperitoneal hemorrhage, or other causes. In 35 per cent of cases, according to Dolan,² and in 40 per cent, according to Morse,⁶ the intrauterine pregnancy will proceed to full term.

Comment

We have reported what we believe to be the first recorded case of combined intrauterine and interstitial pregnancy. A brief discussion on diagnosis and management of this and similar conditions has been presented.

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the mass. Using no. 30 cotton on straight intestinal needles, closely placed mattress sutures were taken anteroposteriorly through the uterus just proximal to the mass. The mass was then coned out of the uterus distal to the mattress sutures. The anterior and posterior muscular flaps thus formed were approximated with interrupted sutures of no. 30 cotton. Reperitonization was accomplished by tacking the right tube over this region with interrupted cotton sutures. The abdomen was closed in layers without drainage. Blood was administered throughout the procedure (a total of 1,500 c.c.), the patient remaining in good condition throughout.

Pathologic report by Dr. W. Putschar was as follows:

There was a mass measuring 5 by 5 by 4 centimeters. On one corner section of the tube was continuous with the mass, and that portion measured 2 centimeters. On the other surface there was a portion of omental tissue firmly adherent to the mass. On the opposite corner from the tube a fresh muscular surface was exposed. On section there was an amniotic cavity 2 cm. in diameter filled with clear yellow fluid and containing a fetus 12 mm. long. The cavity was lined by smooth membrane. The wall measured 0.5 to 0.8 centimeter. The cavity apparently was mainly located in the interstitial portion of the tube, as evidenced by the surrounding myometrium. Lumen contained round, partly necrotic chorionic villi. There were laminated clots and fibrin present. The fairly thick mucosal wall was partly disrupted. Diagnosis: ruptured interstitial pregnancy in right tubal corner sealed off by omentum with fetus of about five weeks.

Because of the enlarged, cystic uterus, it was felt at operation that there was combined pregnancy. This impression was confirmed by the absence of vaginal bleeding at any time, as the decidua should have been cast off after removal of the ectopic pregnancy, had there not been a combined pregnancy. A positive Friedman test on the tenth and eleventh postoperative days served as additional confirmation.

The patient's hospital course was uneventful, and she was discharged on the twelfth postoperative day.

She was followed in the outpatient clinic, and no complications developed. Because of the operative weakness of the uterine cornu, it was felt that cesarean section was advisable, so she was readmitted for operation twelve days before her estimated date of confinement.

On Aug. 13, 1947, she was delivered of a living 6 pound, 4 ounce female child by classical cesarean section. Partial left salpingectomy was performed simultaneously for the purpose of sterilization. She was discharged in good condition on her tenth postoperative day.

Discussion

Combined intrauterine and extrauterine pregnancy is uncommon. Frank⁴ estimates an incidence of once in every 105 ectopic pregnancies. Since it is estimated that ectopic pregnancy occurs about once in every 300 pregnancies, this would place the frequency of occurrence of combined pregnancies at approximately once in every 30,000 pregnancies. There has been some confusion in review of the total number of cases. Sloat and Peterson,⁹ in 1938, arrived at a total of 324 cases. In 1944, Studdiford and Speck,¹¹ using compilations of Mitra and Ludwig, estimated the total as being between 309 and 368 cases. A condition which is more unusual than combined pregnancy is interstitial pregnancy. TeLinde¹² states that prior to 1893 we have had to rely on autopsy reports, but that subsequent to that time the literature has presented approximately 200 cases. Needless to say, both conditions are sufficiently rare to make the chance of their simultaneous occurrence almost negligible. Even more remote is the possibility of such a combination resulting in the delivery of a viable child.

The literature reviewed by the authors suggests that many cases of combined pregnancy are mismanaged because the condition is not kept in mind. Active uterine bleeding does not exclude an ectopic pregnancy. There is danger in depending on curettage of the uterus and the finding of placental tissues in ruling out ectopic gestation. The mortality rate has been highest in those cases in which the outstanding symptoms have been those of intrauterine pregnancy.¹¹

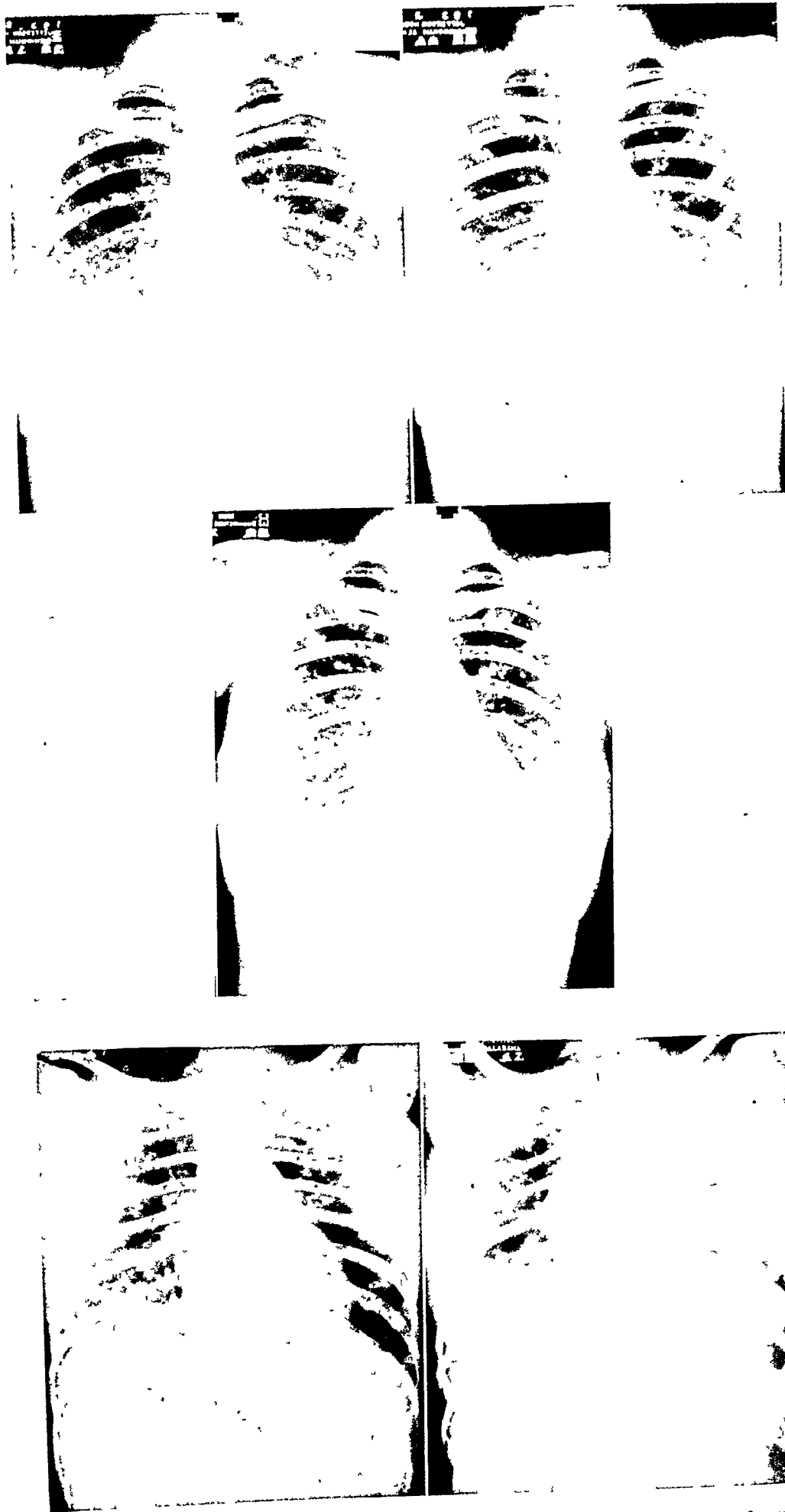


Fig. 2.—Chest plates taken at weekly intervals showing progressive spread of pulmonary metastatic lesions.

CHORIONEPITHELIOMA ASSOCIATED WITH NORMAL PREGNANCY

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CHORIONEPITHELIOMA is a rare, and usually fatal, disease occurring about once in every 13,000 deliveries.¹ Fifty per cent of chorionepitheliomas are preceded by hydatidiform moles and the remainder by abortions, with a few cases being associated with normal pregnancies. The infrequent appearance and grave prognosis of this condition warrant the reporting of an additional case.

This patient, A. M. D., hospital No. 30,839, an 18-year-old Negro female, gravida ii, para i, delivered a normal child Dec. 9, 1946. Normal menstrual periods were resumed in January, 1947, and recurred at monthly intervals until May 17, 1947. She was admitted to the Jefferson Hospital Sept. 21, 1947, complaining of lower abdominal cramps and bleeding. Examination at that time revealed a pregnancy of approximately two and one-half months, and a diagnosis of threatened abortion was made. She was treated with sedation and bedrest and was discharged. The patient was readmitted Oct. 6, 1947, at which time she was again complaining of abdominal cramps and vaginal bleeding and was treated with sedation and bedrest. Examination at this admission revealed several small ulcerative areas on the anterior vaginal wall. She was next seen in the outpatient department one week later complaining of profuse vaginal bleeding that had begun during the night. Hemoglobin was 33 per cent, with 1,780,000 red blood cells, and she was admitted to the hospital where examination revealed multiple, friable lesions of the anterior vaginal wall that bled profusely when touched.

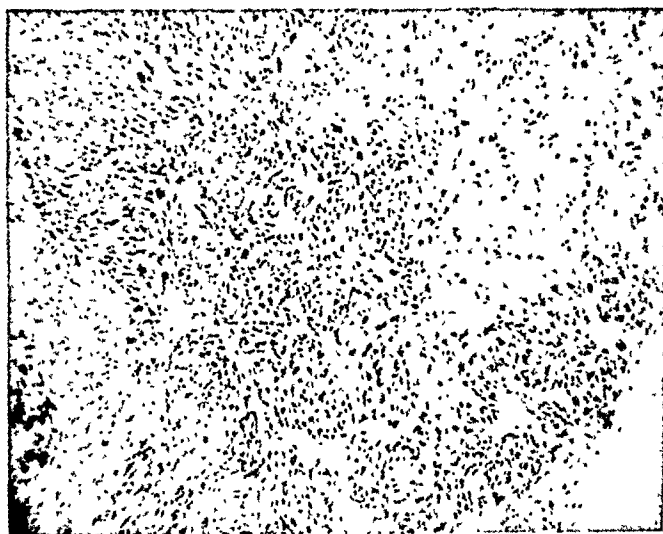


Fig. 1.—Low power study of vaginal biopsy showing malignant trophoblastic cells, mostly syncytial.

Biopsies were taken and reported as chorionepithelioma. The patient at this time was approximately four and one-half to five months pregnant. Fetal heart tones were heard, and a flat plate of the abdomen revealed a small fetal skeleton present. Chest plates showed the presence of metastatic lesions in the lungs. At this time the patient complained of coughing with one episode of hemoptysis.

A total hysterectomy and a bilateral salpingo-oophorectomy were done on Nov. 6, 1947, with spinal anesthesia. The patient stood the procedure well. The fetus, in spite of deep x-ray therapy, was still viable and was approximately five and one-half to six months old; it expired shortly thereafter. Blood studies on the fourth postoperative day revealed a 32 per cent hemoglobin for which she received 1,500 c.c. of blood. Except for a small abscess of the skin and subcutaneous tissue in the lower end of the incision, her immediate post-operative course was uneventful. X-ray therapy to the pelvis was continued, and radiation to the lungs begun. The patient had two episodes of hemorrhage from the vaginal implants which required packing. Further x-ray studies revealed diffuse metastatic infiltration throughout both lung fields. She had a rapid downhill course and died Dec. 4, 1947, on the twenty-seventh postoperative day. At the time of her death the patient had received a total of 4400 r to her pelvis directed through two anterior and three posterior ports, while 500 r had been delivered to her chest before she expired.

The pathologic report in this case was extremely interesting. The placenta was examined closely by the pathologic department, and a small area of abnormal trophoblastic activity was noted in one villus. The remaining multiple sections through the placenta were entirely negative. Tumor cells were also found within a blood vessel of the uterus at the placental site. Remaining sections through the uterus were entirely negative.

This case brings up the question of where the choriocarcinoma originated. This patient had had a normal pregnancy ten months previous to the present pregnancy. She did not nurse her baby, and normal menstrual periods were resumed. We have no history of miscarriage in the ten months between pregnancies. It is quite unusual to see a choriocarcinoma associated with normal pregnancies. The first evidence of an abnormal condition in what seemed to be a normal pregnancy was the appearance of vaginal metastasis when the patient was approximately three and one-half to four months pregnant. The prognosis in choriocarcinoma is very poor. The treatment of choice is usually total hysterectomy, but even this in early cases offers a poor outlook. This patient on admission was in no condition to stand a major operative procedure. When the patient was finally in shape, a total hysterectomy was carried out in the face of pulmonary metastasis.

Choriocarcinoma is a rapidly metastasizing tumor and very often primary lesions are not found in the uterus.² This is well demonstrated in this case because after multiple sections were made through the uterus only one area of malignant cells was noted and these were within a blood vessel. The finding of malignant trophoblastic activity within a small area of the placenta leads us to suspect this as the primary lesion.

This unusual case of chorionepithelioma associated with a normal pregnancy and probably originating in the placenta is presented.

This has impressed upon us very forcibly the necessity for serial sections in determining pathology in obscure cases, otherwise this would not have been found in this case.

We were unable to obtain an autopsy.

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1. Schumann, A. B., and Voegelin, A. W.: *AM. J. OBST. & GYNEC.* 34: 267, 1937.
2. Hertig, A. T., and Sheldon, W. H.: *AM J. OBST. & GYNEC.* 53: 1, 1947.

It was the opinion of the staff that the treatment of choice in this case would be total hysterectomy, but because of the severe anemia, she was not in condition for such a procedure. It was therefore decided to build up the patient as rapidly as possible with transfusions and

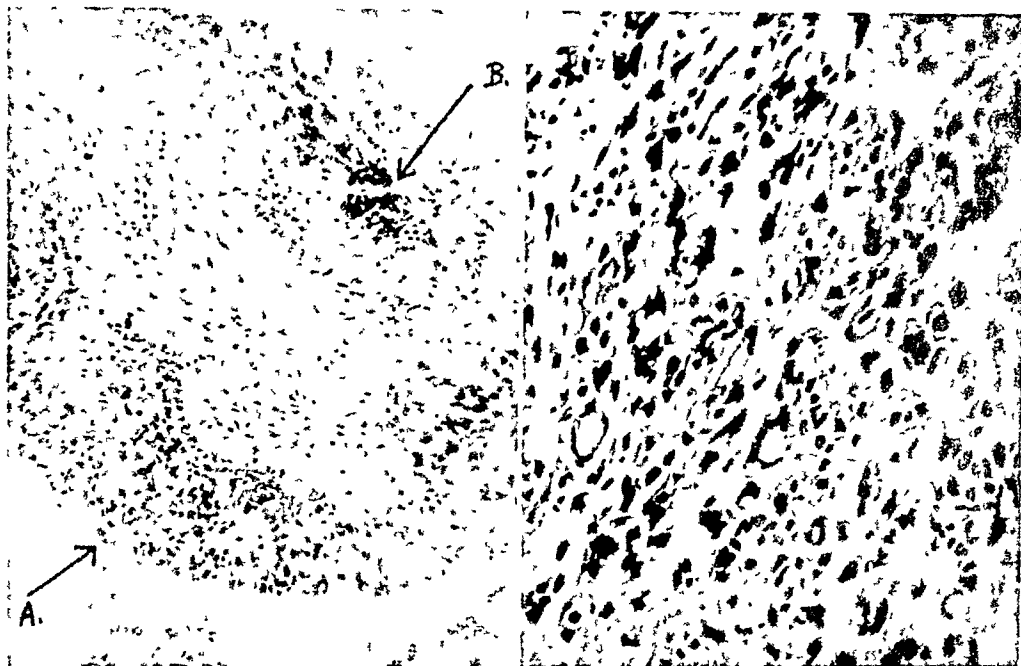


Fig. 3.—Section from the placenta showing trophoblastic hyperplasia and anaplasia. (Low and high power.)

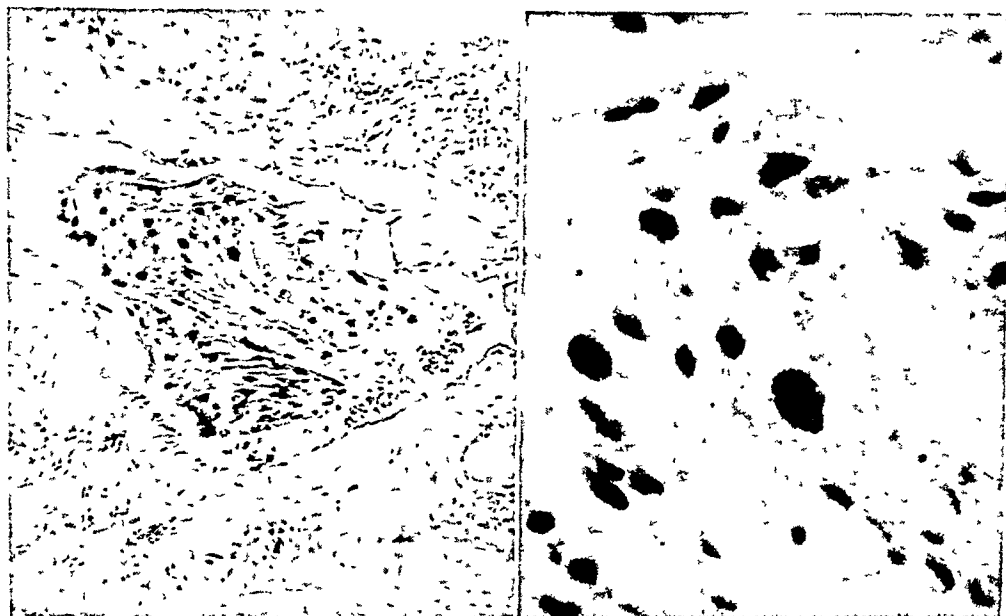


Fig. 4.—Section from the uterus showing malignant cells within a blood vessel. (Low and high power.)

supportive treatment. In the meantime, deep x-ray therapy to the pelvis was begun. She was given 3,500 c.c. of blood during the next twenty-five days before her blood picture attained a level high enough to make surgery possible. Chest plates taken at weekly intervals showed definite metastatic lesions in the chest that were progressive in nature.

EPISIOTOMY SCISSORS

FRED HAUFRECT, M.D., HOUSTON, TEXAS

THESE scissors are designed to facilitate the performance of episiotomy, to reduce the amount of blood loss, to judge better the extent of the incision necessary and to protect the fetal head.

Conventional scissors used for episiotomies cut forward, and must be directed downward, or down and laterally, depending upon the type of episiotomy. The handles do not conform to the fetal head as the latter bulges between the labia. In a forceps delivery, there is a more obvious interference by the handles of the forceps.

To offset these difficulties, episiotomies are often done early before crowning, or before the forceps are applied. In such instances, there must be an increase in the amount of maternal blood loss due to the increased interval from the time of the episiotomy to the time of its repair. Also, the presenting part does not bring sufficient pressure to bear upon the perineum to reduce the local blood supply. The opposite of the latter is clearly demonstrated when forceps are applied and the episiotomy is made as traction is applied to the forceps.

An episiotomy done early with ordinary scissors may be either too short or too long. It is more difficult to judge the relationship of the size of the fetal head to the give of the perineum.

This new type of scissors consists of two blades which make an acute angle with the handles. The internal blade (Fig. 1, B) terminates in a blunt tip.

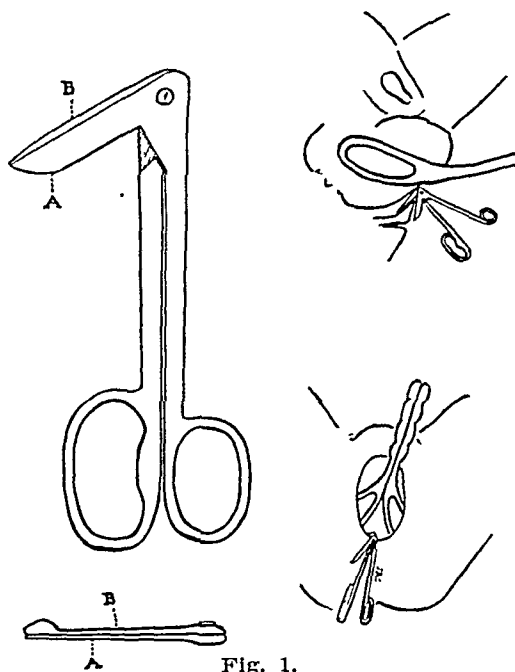


Fig. 1.

When holding these scissors in the conventional manner, the operator cuts in a direction toward himself. The thumb grip controls the external blade (A) which comes in contact with the skin surface of the perineum.

These scissors permit the operator to do the episiotomy at a later period, when the head is crowning in normal deliveries or when forceps are used. This is due to the fact that the handles of the scissors point almost perpendicularly to the skin surface of the perineum, away from the presenting part or handles of the obstetric forceps.

The blunt-tipped internal blade (B) is directed between the fetal head and the perineum with pressure toward the perineum. This avoids injuring the fetal head. There will be no need to insert a finger into the vagina to guide the blade.

I have employed this instrument for almost two years at St. Joseph's Infirmary.

PENICILLIN TREATMENT IN PRENATAL SYPHILIS

CONRAD L. GOSSELS, M.D., MOUNT JACKSON, VA.

THE importance of penicillin treatment in syphilis is well established. Numerous reports prove the advisability of penicillin treatment in different phases of this disease, although no uniformity of opinion has been reached about dosage and best time for treatment. However, there seems to be no doubt about the effectiveness of penicillin in prenatal syphilis as to results for mother and child.

The following case history illustrates the changes in treatment and outlook very clearly:

Mrs. M. N. was 35 years old when she saw me the first time in 1945. She had recently delivered a stillborn baby, four weeks before term. Not satisfied with the diagnosis "kidney trouble" given to her as cause of the stillbirth, she requested a general checkup. Her history did not reveal any venereal infection. On questioning, she remembered that her mother had some positive blood tests years ago, but no details were known. She never was sick. In 1939 she had married. Her husband had never seen a doctor.

Her obstetric history was: her first pregnancy occurred in 1940, and resulted in delivery at term. Baby died at the age of one year. Her second pregnancy in 1941, was terminated by abortion in the third month of pregnancy. Her third pregnancy, in 1943, was terminated in the sixth month. In 1945 she delivered a stillborn baby one month before term. In 1941, when the first baby died, a positive Kahn test was found and treatment started. This treatment was continued over two and one-half years, with an interruption of four months. Three blood tests were taken during this period, but details were not available. The first baby was treated, too, as soon as during a "throat infection" the syphilitic origin was established. The result of blood test when treatment was discontinued is not known. Length of treatment and dosage apparently were not sufficient.

The general checkup in 1945 was completely negative. There were no signs of syphilis present. Kahn test was positive. Antisyphilitic treatment was given, and continued with the cooperation of the patient. In October, 1946, she became pregnant again. At that time the Kahn test was still positive. In February, 1947, twenty-four injections of Mapharsen (14.4 Gm.) and 30 injections of bismuth subsalicylate (4.0 Gm.) had been given. In February, 1947, the fourth month of her pregnancy, penicillin treatment over ten days with 2,800,000 units was given. No further treatment afterwards was considered necessary. In July, 1947, a normal girl was delivered. Mother and baby are in good health at the time of this report, fourteen months afterwards.

TABLE I. SEROLOGIC TESTS

MOTHER										BABY	
1945	1946		1947							1947	1948
12/22	4/24	12/5	4/28	6/12	7/15	8/1	9/2	12/2	6/1	7/16	1/29
plus	plus	plus	doubtful	plus	plus	doubtful	neg.	neg.	neg.	neg.	neg.
			0-1-1	4 u	2 u	±2 3					

The serologic tests are shown in Table I. The first sign of a change in the serologic tests was evident in April, 1947, two months after penicillin treatment. But the serologic test did not change to negative before September, 1947, seven months after penicillin treatment and stayed negative thereafter. The good health of the normal baby and the continuance of the negative serologic test in the baby is a gratifying result for the long treatment the mother undertook. Four times pregnancy resulted in death of the baby or fetus, respectively. The fifth pregnancy gave the 37-year-old woman a healthy baby. The effectiveness of penicillin treatment in prenatal syphilis is corroborated by this case.

not any projection on the peritoneal aspect and nothing that could be palpated. During a laparotomy late in obstructed labor, the junction of the two segments is not a noticeable thing and it certainly does not project on the surface of the uterus. Such operations are rare in this country, but Dr. Mahmoud Ismail Bey, Professor of Obstetrics in the University of Cairo, in a personal letter, says, "As regards my opinion about the 'projecting' ring of Bandl at the junction of the upper and the lower segment, I can say that I have done cesarean sections often for women long in labor in whom the lower segment was over-stretched but I did not notice or feel such a projecting ring. In many cases the top of the bladder was high enough to be felt as a ridge." There are several excellent specimens

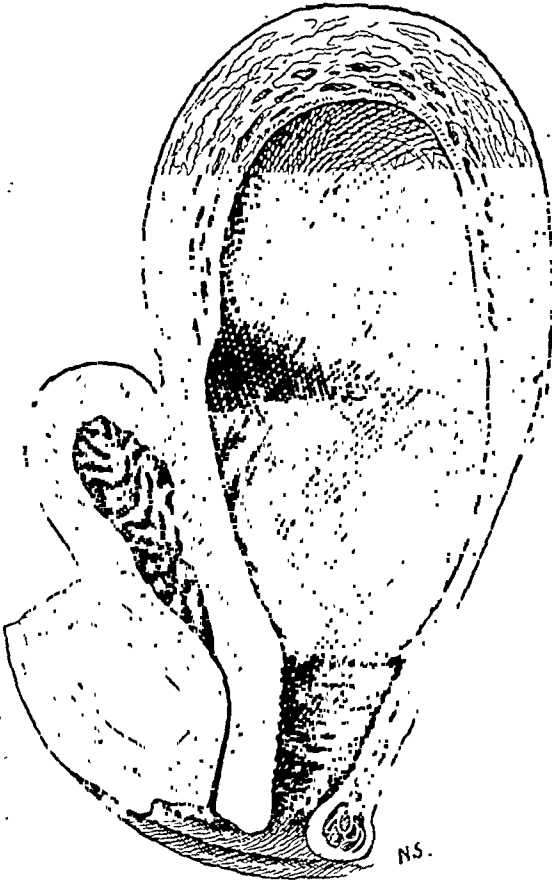


Fig. 1.

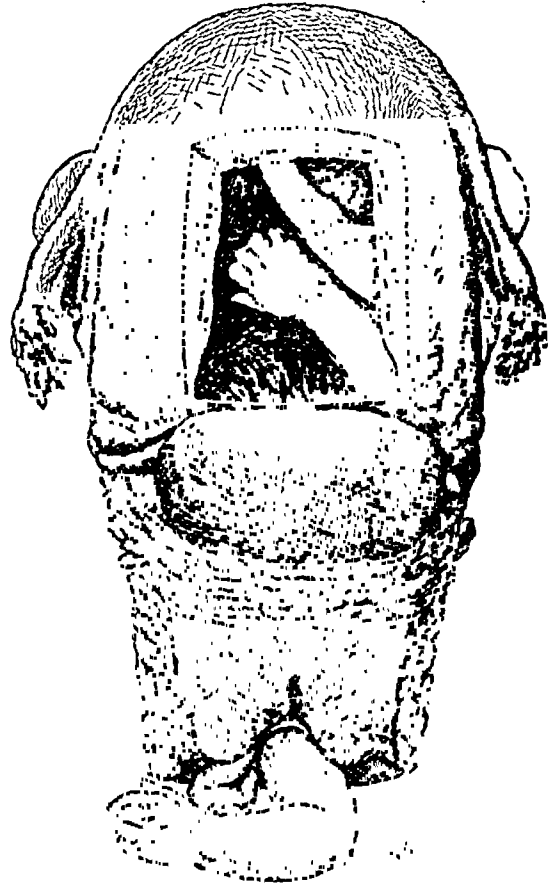


Fig. 2.

Figs. 1 and 2.—Two sketches from a postmortem specimen to show that the ring of Bandl does not form a palpable ridge but the raised edematous bladder does form an easily palpable mass which rises during labor.

of the uterus in tonic retraction in the famous Mahfous collection in the museum of the Kasr el Aini Medical School in Cairo, which confirm my views that it is improbable that anyone has ever palpated the junction of the upper with the lower segment or felt it as a projecting ridge. Yet, for years it was taught that the retraction ring could be palpated through the abdominal wall and could be noticed to rise higher and higher in the lower abdomen while the patient was watched. In my opinion the ridge which they palpated was the top of the edematous bladder which is attached to the lower segment and would certainly be found to get higher as the obstructed labor progressed. Figs. 1 and 2 from a postmortem specimen in the Mahfous collection show that this is the truth.

The upper segment having become retracted and thick and the lower segment thinned, nothing will get them back to their normal state except the delivery of the baby and the involution of the uterus. No drug could possibly alter this condition back to the normal and, thus, as a corollary, if the use of a drug such as morphine appears to alter a

Correspondence

Uterine Overaction and Its Nomenclature

To the Editor:

I am addressing this letter to you because the various types of overaction of the uterus are difficult to define accurately and different writers use the same name for different clinical entities; this is especially the case when uterine rings are mentioned.

In 1913 I read a paper at the Royal Society of Medicine entitled "The Contraction Ring as a Cause of Dystocia." In it, scattered reports of cases were collected from the literature and I described a specimen which I had obtained by removing the unopened pregnant uterus from a patient in labor. In England, the condition is known as a contraction ring; in the United States, Rudolph and Ivy call it a constriction ring. I think the term contraction ring has the advantage that, in midwifery, contraction is followed by relaxation sooner or later.

At present, the terminology used to describe the various types of uterine rings is in a chaotic state; Rudolph and Fields¹ state that the various current names are: ring of Bandl, contraction of the ring of Bandl, contraction ring dystocia of White, retraction ring dystocia of Pride, simply contraction or retraction ring, uterine contraction ring and constriction ring of Rudolph. Pierce Rucker² states that I was the first to differentiate a contraction ring from a retraction ring. This is the reason why I am writing to you on the subject, as I do not seem to have made the differences clear; as an example, I need go no further than the same page of Pierce Rucker's paper where he quotes H. W. Johnson's contribution on "Delay in Labor Caused by Mild Degrees of Bandl's Ring." In my opinion, this is an impossibility as the retraction ring of Bandl could never cause delay in labor.

In obstructed labor, the fetus acts as a splint which keeps the length of the uterus constant and, since each contraction in the second stage of labor is followed by slight retraction, it follows that in the course of hours the upper segment becomes retracted and thicker; since the fetus is keeping the length of the uterine cavity constant, the lower segment must become thinner. There is no other way for the upper segment to become thicker while the length of the uterus remains constant except by thinning of the lower segment. The importance of the fetus acting as a stretcher and maintaining the length of the cavity of the uterus is stressed, as it is an important part of the process of obstructed labor. It is interesting to speculate what would occur if the fetus were absent, as in the utterly improbable case of the uterus trying to expell a large hydatidiform mole through an occluded cervix.

Seeing that the essential condition of the uterus of obstructed labor is one of retraction, it is usual to call it "tonic retraction of the uterus," although, unfortunately, it is sometimes referred to as "tonic contraction." This is a misnomer as, in midwifery, contraction suggests a subsequent relaxation which never occurs in the uterus of obstructed labor, so it is better to speak of either the uterus of obstructed labor or tonic retraction.

Tonic retraction is a slow process taking six or more hours in the second stage to develop. Except in the rare cases of pathological obstruction of the cervix (e.g., a cervical fibroid), tonic retraction does not occur in the first stage of labor or when the membranes are intact; it is a late second-stage phenomenon and is caused by disproportion. The mother's general condition is bad, with raised pulse and temperature, the abdomen is very tender and, per vaginam, the presenting part has a big caput and is fixed. As the placental site is continuously retracted, the fetus dies from lack of oxygen and so the fetal heart is never heard during tonic retraction.

The junction of the retracted, thickened upper segment with the thinned, tense, distended lower segment is the retraction ring or ring of Bandl. The thickened upper segment takes 2 cm. or more gradually to merge into the thinned lower segment, but there is

Textbooks tell us that one of the causes of tonic retraction is the use of stimulants to uterine action, such as ergot or Pitocin, but this is improbable. Tonic retraction is essentially a slow process and insidious in its onset, whereas the action of Pitocin is prompt. It is possible that oxytocic drugs may increase the force of uterine contractions and so, in the presence of an obstacle to delivery, make the onset of obstructed labor quicker than it otherwise would have been, but that is all. In the absence of disproportion, all that oxytocics could do would be to produce an irritated uterus, i.e., a generally contracted uterus where the whole uterus is contracted but there is not any thinning of the lower segment. Another way in which a generally contracted (irritated) uterus can be produced is by manipulations, for example, when attempts are made to dilate the cervix manually or when the forceps is applied to the head above the brim and unsuccessful efforts made to deliver the child. In such patients, it is sometimes found that the uterus does not relax and such a case can easily be mistaken for one of tonic retraction, but, after an interval, the uterus is found to be contracting and relaxing normally. A little consideration will show that tonic retraction could not have been present in such patients because it comes on gradually and is never followed by relaxation or by normal uterine action; also, the lower segment is not thinned or tense and the general condition of a patient with a generally contracted uterus remains good. Morphine will assist an irritated uterus to become normal again more quickly than it otherwise would. Although the long-continued contraction of the irritated uterus makes it feel hard, the contraction does not seem sufficient always entirely to stop the circulation through the placental site and so a living child may be obtained after an interval. In tonic retraction the circulation through the placental site has failed and so the child is dead.

A contraction ring is a localized contraction of the uterus which frequently forms over a depression in the child's outline but may be below the child. It occurs in the first, second, and third stages of labor and even before there are signs that labor has started. Hence, it is not the result of labor obstructed by disproportion, and, if disproportion happens to be present, its presence is a coincidence and not a causal factor. The body of the uterus above the ring continues to contract and relax as in a normal labor. The patient's general condition is quite good—several of my patients had a pulse rate of 80. The circulation through the placental site is maintained and so the child is alive.

The cause of the condition is obscure; the causes mentioned in my original article are not truly etiological factors. A contraction ring does cause delay in labor.

Occasionally a contraction ring can be palpated through the abdominal wall as a depression running across the lower part of the uterus. It is usually tender and sometimes the patient states that she notices the discomfort of a uterine contraction first in the region of the ring. If the head is presenting, it is lifted up during a pain and so becomes more mobile from side to side as first described by Gilliatt. On vaginal examination, signs of disproportion are absent. In the majority of cases, the failure of traction by the forceps is the first thing to show that an abnormality is present. Moreover, when the forceps has drawn the head down, it recedes to its original level in the pelvis as soon as traction is stopped. The reason for this recession of the head is that the forceps pulls down the whole uterus containing the child and the resilience of the cardinal ligaments takes the uterus and its contents back to their original level as soon as traction is stopped. In a similar way, the head does not descend during a pain. These signs are an indication for passing the hand into the uterus when the ring will probably be felt round the child's neck.

The treatment of contraction rings has been fully discussed by Rudolph in various papers and so will not be further touched on here.

CLIFFORD WHITE.

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1. Rudolph, Louis, and Fields, Charles: *AM. J. OBST. & GYNEC.* 53: 796, 1947.
2. Rucker, Pierce: *J. Mt. Sinai Hosp.* 14: 576, 1947.

tonically retracted uterus into a normally acting one, it immediately proves that the uterus was not tonically retracted but that some other condition, such as an irritated uterus, was present. Morphine is most valuable in slowing uterine action and thus preventing the rapid progress of retraction but it cannot alter the condition already established. If this is recognized, it will prevent people from stating that tonic retraction has been cured by any treatment other than the removal of the fetus that was splinting the uterine cavity.

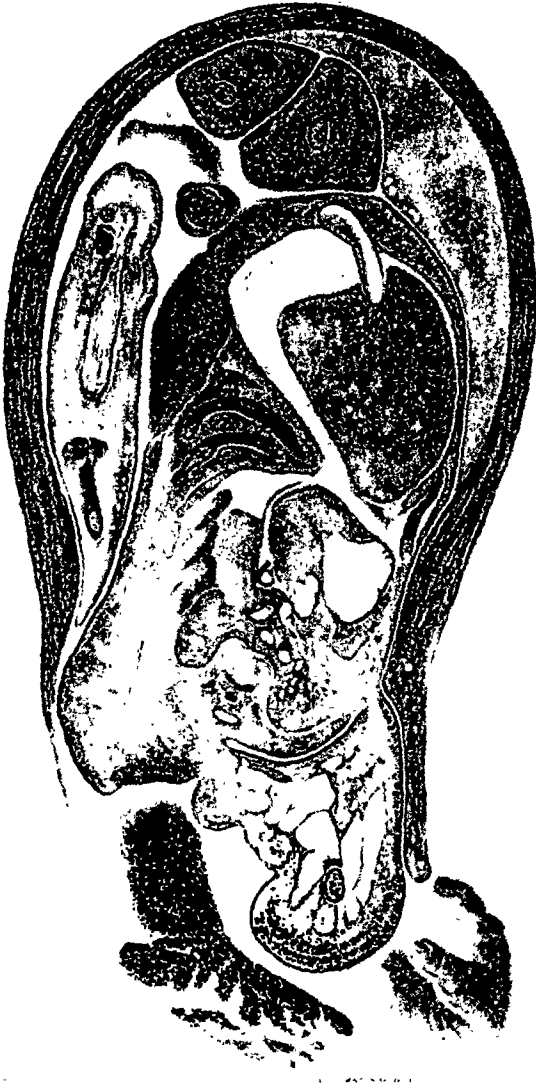


Fig. 3.

Fig. 3.—Mesial sagittal section of uterus with fetus in situ. The child was presenting by the shoulder, and a foot had been brought down in an unsuccessful attempt to perform version. The contraction ring can be seen running obliquely across the uterus. The upper uterine segment is not thickened and the presenting part was not fixed in the brim of the pelvis.

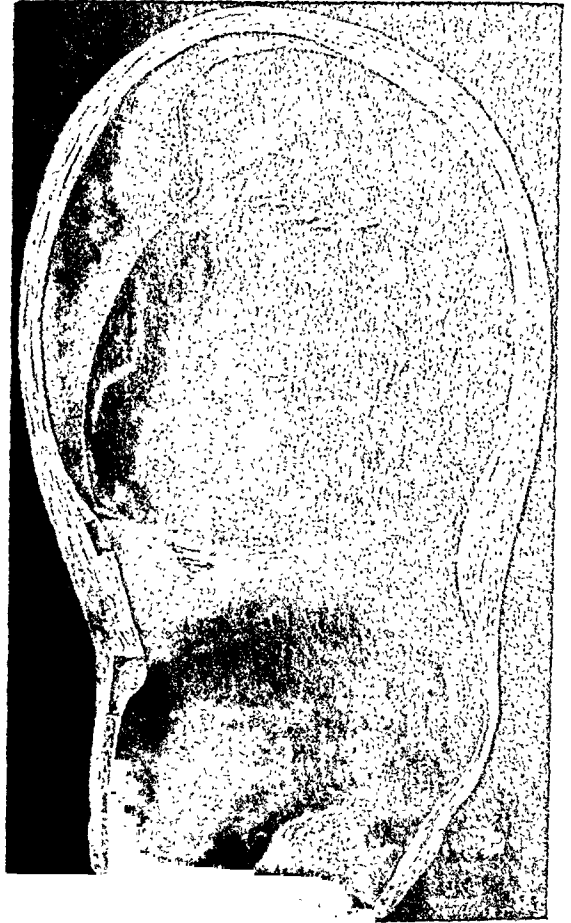


Fig. 4.

Fig. 4.—Mesial sagittal section of uterus removed during labor, showing contraction ring which caused dystocia.

The end of untreated obstructed labor is death, either from exhaustion or from rupture of the uterus; it is perhaps justifiable to regard tonic retraction as Nature's method of killing fairly quickly a patient with an insuperable obstacle to delivery. Fortunately, secondary uterine inertia does not occur in the second stage of a labor complicated by bony obstruction; if it did, the patient's agony would be prolonged for many days. Yet any examiner knows how frequently students state that there are two alternatives in a case of obstructed labor, either tonic retraction or secondary uterine inertia. Luckily, the statement is not true.

Department of Reviews and Abstracts

Selected Abstracts

Cancer, Malignancies

Cusmano, L.: Distribution of "A" Proliferative and "B" Regressive Nuclei in Cancer Tissue, *Tumori* 37: 108, 1947.

Cusmano reports in this paper relative frequency of proliferative "A" and regressive "B" nuclei in five cases of cancer of the cervical canal, four cases of cancer of the intra-vaginal portio of the uterus, and in three cases of carcinoma of the fundus.

The material was prepared by his crushing carminacetic method and by Feulgen microchemic reaction for demonstration of timonucleinic acid. Ten different portions of each tumor were examined and cellular areas were selected for analysis. Frequency of mitotic figures appeared to be closely correlated with the amount of proliferative nuclei. Mitoses were practically absent from areas showing prevalence of regressive nuclei.

Regressive nuclei were prevalent in the three cases of cancer of the fundus. Proliferative nuclei, instead, predominated in the five cases of cancer of the cervix, while in the cancer of the portio (which Italian pathologists classify separately from the cancer of the cervix) proliferative nuclei were more numerous in one case, regressive nuclei prevalent in the remaining cases.

No definite correlation was evident between degree of maturity estimated from the histologic pattern and distribution of proliferative versus regressive cells.

GEMMA BARZILAI.

Cusmano, L.: Mitotic Figures in Cancer of the Fundus and Cervix, *Tumori* 37: 185, 1947.

Cusmano reports findings of mitotic figures observed in nine cases of cancer of the cervix and in three cases of cancer of the fundus, prepared with the crushing acetic-carminic method and Feulgen's microchemic reaction.

Normal and abnormal mitoses have been found present in the material. Prophase, prometaphase, the long-lasting early phases of mitosis are frequent, anaphase, and telophase, the short-lasting phases of division of the nucleus into daughter nuclei (when details of the process are most evident) are rare.

Neither prophase nor metaphase showed appreciable deviation from corresponding phases of division in healthy cells; typical early aspects of prophase similar to the proliferative "A" cell nuclei, but with some incipient dissolution of the nuclear membrane and more condensed appearance of the chromomeres were seen, as well as late prophase showing dissolution of nuclear membrane and split chromosomes, and metaphase with evenly distributed chromosomes at the equator of the nucleus.

Anaphase and telophase, however, were present showing atypical aspects: anaphase and telophase with aploid, tetraploid and polyploid number of chromomeres, and also showing definitely deviated features such as deletion of parts of the individual chromosomes, inversions, and translocation of single or multiple individual chromosomes, were seen. Altogether, 196 mitoses were observed; 32 appeared normal, 54 showed irregularities in the number of the chromosomes, but only 10 showed definite deviations from healthy nuclei, such as deletion, inversion, and translocation of chromosomes.

This significant paper throws light on the interpretation of mitotic figures in cancer cells; it shows the similarity of proliferative "A" nuclei to early prophase and gives evidence of the rarity of mitosis showing features that can really be considered pathognomonic for a neoplastic growth.

GEMMA BARZILAI.

The Significance of the Nuclear Structure in the Vaginal Secretion Cells as a Means for Cancer Diagnosis

To the Editor:

The papers by Papanicolaou, G. N. (AM. J. OBST. & GYNEC. 51: 316, 1946) and by Ayre, J. E. (AM. J. OBST. & GYNEC. 53: 609, 1947), which emphasized the importance of the nuclear characters for recognizing the neoplastic elements, stimulated me to extend my investigations, which had reached the study of the nucleus of the malignant cell (Tumori 33: 10, 107, 178, 1947, and Quaderni di Clin. Ost. e Ginec. 2: 9, 1947), to an interpretative complement of the observations carried out in them.

Meanwhile, Papanicolaou took into consideration the cell as a whole, with techniques not exclusively designed for nuclear examinations. I was stimulated by the observation that the complex of the characters denoting malignancy is indicated by abnormalities, specifically connected with the metabolism of nucleic acids. From the views expressed by Caspersson, T., and Santesson, L. (Acta Radiol. Suppl. 46: 1, 1942), and by Koller, P. C. (Nature 151: 244, 1943, Brit. J. of Cancer 1: 38, 1947, and Symp. Soc. Exper. Biol. 1: 270, 1947), I reached the conclusion that the neoplastic cells are recognizable from the structure of the resting nucleus. This is distinguishable in two main phases, i.e., when they are overcharged with thymonucleic acid (termed A, with small and not always recognizable nucleoli), and undercharged with thymonucleic acid (B, with well-developed nucleoli). It is clear that the former correspond to the prophaselike cells noted by Papanicolaou. Generally speaking, my conclusions do not differ from those expressed by the American author. Only I go further, interpreting the A nuclei as the resting stages of proliferating cells, and the B ones as belonging to cells in a preneurotic stage. Finally, I proved that both cellular types are generally mixed together in a tumor, so that I do not, therefore, agree that the B cells are typical for distinct tumors. The observation of mitoses does not often offer any particular interest for diagnosis, owing to the rarity of the mitosis itself and its frequent normality.

The technique used by myself is based upon the compression, as adopted by the chromosome investigators and not on the simple smear. By this means, the cells (previously fixed with two-thirds 96 per cent alcohol, one-third acetic acid for many hours, where the secretion may remain indefinitely, practically without damage) are transferred into a drop of saturated acetic solution (50 per cent acetic acid in distilled water) and carmine powder. The material must remain there for one to two hours. Later, by means of a pipette, it is transferred to a slide, previously covered with a thin film of egg albumin and dried. A cover slip is put on and pressed down without smearing. Finally, by means of a needle, the material is crushed and the superfluous liquid absorbed with blotting paper. This preparation must be observed by green light. A technique is also employed for making the slides permanent, which is too long to refer to here. The microscopic field offers for observation naked nuclei, in the best conditions for revealing the finest structures. The Feulgen reaction can be substituted for the acetocarmine.

The technique used by other authors does not permit observation of the nucleus under favorable conditions, because it gives only a general appreciation of the cell as a whole. For that reason my technique may be more advisable, owing to the fact that the diagnostic characters are seen chiefly in the nucleus.

The technique which I have described must be considered, therefore, as a specialization of that proposed by Papanicolaou, who was the first to give consideration to the value of the cellular structure for diagnostic purposes.

This method has been used with success for making diagnosis of uterine tumors. Up to the present time, the results of the nuclear diagnosis are in agreement with the histologic and chemical features.

DR. LUIGI CUSMANO.

CLINICA OSTETRICA E GINECOLOGICA
DELLA UNIVERSITA DI PARMA
ITALIA
MAY 18, 1948.

the cecum was involved. In a study of the pathologic specimens at the Clinic, two specimens of endometriosis of the cecum were found, which clinically could not be distinguished from carcinoma.

In the case reported, the patient was a woman 29 years of age. Her menstrual periods had been regular, the flow lasting four to five days. For six years before admission to the Clinic, she had had premenstrual pain that had subsided when the flow started. At the time of the last menstrual period before admission, pain had been more severe and was accompanied by abdominal tenderness that localized in the right lower quadrant. Six days before admission, pain recurred, at first generalized over the lower abdomen, then localizing in the right lower quadrant, accompanied by nausea and vomiting; two days later, the regular menstrual period began. On admission to the Clinic, nausea, vomiting, diarrhea, pain, and tenderness in the right lower quadrant were present. The patient was kept under observation for seven days, but, as nausea and anorexia persisted and there was slight pain and tenderness over the McBurney area, operation was done. The uterus was of normal size and position, but showed a subserous fibroid on the posterior wall; the left ovary was enlarged owing to a simple cyst from which clear fluid was expelled on puncture; no endometrial implants were found. The cecum was bound in the pelvis by adhesions that appeared to be recently formed. There was a slight inflammatory reaction around the appendix and appendectomy was done. The base of the appendix was inverted. A hard nodule was palpated in the wall of the cecum and was considered to be possibly malignant. Immediate biopsy of a small section showed an endometrioma; and a local wedge excision including normal tissue well around the tumor was done. No further signs of endometriosis were found. The patient made a good recovery; and subsequent menstrual periods have been normal and painless. HARVEY B. MATTHEWS.

Murphy, G. H., and DuShane, J. W.: Mesodermal Mixed Tumor of the Vagina, Proc. Staff Meet. Mayo Clin. 23: 22, 1948.

In the case reported, the patient was a child of 33 months of age. A year previous to her admission to the Clinic, blood had been noted around the vulva and examination showed a tumor of the vagina. This tumor was removed and reported to be histologically a botryoid sarcoma (rhabdomyoma). Radium and roentgen-ray therapy was employed postoperatively, but there was a recurrence of vaginal bleeding after several months, for which more radiation therapy was employed. When admitted to the Clinic, the child showed no signs of distress. Examination showed a mass in the vagina, and at operation a soft polypoid tumor was found to fill the vagina. Frozen sections showed a high-grade malignancy, but, as the tumor had infiltrated the vaginal wall, only local removal was done. The tumor had the appearance of a group of fused polyps—the typical “botryoid” tumor. Histologically, it consisted of myomatous-appearing network, with some cellular areas; some of these areas showed spindle cells with mitotic figures, others showed young striated muscle cells with some embryonic myoblasts; there was no cartilage or bone, but some areas of the tumor contained collagen. This is the first case of a tumor of this type observed at the Mayo Clinic.

Mesodermal mixed tumors occur in the uterine body, the cervix, and the vagina. The reports in the literature on the nature and incidence of these tumors are confusing. The relative incidence of the tumors in the various sites is difficult to determine, but the vaginal tumors appear to be the most common. The vaginal tumors have been found only in young children, mostly in those under three years of age. The prognosis in mesodermal mixed tumors, whether of the uterus, cervix, or vagina, is bad; the mortality has been given as 95 per cent; the prognosis in the case reported is considered to be “extremely grave.”

HARVEY B. MATTHEWS.

Grattarola, R.: Chromosomes and Nucleoli in Human Cancer Cells During X-ray Treatment, Tumori 21: 321, 1947.

In the Department for Cellular Pathology of the Medical School of Milano, Grattarola studied the nuclear changes occurring in human cancer during x-ray treatment with Feulgen, Unna, and Barigozzi-Cusmano staining procedures.

Cusmano, L.: Nuclear Structures in Normal Villi, Hydatidiform Mole and Chorionepitheliomas, La Ginecologia Scritti in Onore del Professor E. Cova.

In this paper, Cusmano reports observations made on the chorionic epithelium of normal placental villi, simple hydatidiform moles, and chorionepitheliomas stained with his own carminacetic dye and treated with Feulgen microchemic method which reacts positively only with the timonucleinic acid present in the chromomeres.

In normal villi, chorionic epithelium appeared to have uniform elliptical nuclei, with regular nuclear membrane, intensely colored and Feulgen-positive, regularly disposed granules corresponding to chromomeres, and a single large, round, Feulgen-negative nucleolus.

In the hydatidiform mole, nuclei show striking variation in shape; some are round, some are elliptic; most of them have a coarse chromoneme with intensely stained granules, giving a strongly positive Feulgen reaction, and one or two faintly stained and Feulgen-negative nucleoli. These nuclei definitely recall the "A" nuclei of proliferative cells of neoplastic tissue. They show, however, a more marked content of timonucleinic acid.

Among these proliferative nuclei, some identical with the regressive "B" cells of neoplastic tissue are seen and faintly show chromomeres and large clumpy Feulgen-negative and intensely red-stained nucleoli.

In the chorionepitheliomas, proliferative "A" nuclei and regressive "B" nuclei are evident and are identical to those seen in cancer tissue.

GEMMA BARZILAI

Massey, E., Dockerty, M. D., and Masson, J. C.: Malignant Lesions of the Uterus Associated With Estrogen-producing Ovarian Tumors, Proc. Staff Meet. Mayo Clin. 23: 63, 1948.

Two cases are reported in which adenocarcinoma of the uterine fundus was associated with an estrogen-producing tumor of the ovary—granulosa-cell tumor in one case and theca-cell tumor in the other, both of which showed areas of malignant degeneration. These two cases bring the number of malignant lesions of the uterus associated with estrogen-producing tumors of the ovary observed at the Mayo Clinic to 15 cases. In 87 estrogen-producing tumors of the ovary observed at the Clinic, the incidence of malignant tumors of the uterus was 17.2 per cent, or, excluding two cases of cervical carcinoma, 14.9 per cent. These figures are in close agreement with similar series reported by others. Several clinical and pathologic observations indicate that malignant lesions of the endometrium do not develop without accompanying hyperestrinism. Only one case has been reported (by Fremont-Smith and his associates) in which proved malignancy of the endometrium followed prolonged estrogen therapy for menopausal symptoms. It is probable, however, that many women have received equally prolonged estrogen therapy without developing carcinoma of the uterine fundus. The occurrence of episodes of uterine bleeding in such cases often leads to discontinuance of the estrogen therapy or reduction in dosage.

In the discussion of this report, Dockerty stated that, in the series of granulosa-cell and theca-cell tumors of the ovary observed at the Clinic in which the incidence of uterine carcinoma was 17.2 per cent, the incidence in 55 postmenopausal patients was 27.3 per cent, an incidence more than 100 times as high as would occur if the two lesions were merely coincidental. Granulosa- and theca-cell tumors of the ovary rarely recur after local removal or metastasize if well encapsulated at the time of operation; and uterine carcinoma is rarely associated with these tumors in patients under fifty years of age. Therefore, local removal of these tumors when encapsulated is indicated in younger women; but if the tumor is poorly encapsulated or ruptured or the patient has reached the menopause, panhysterectomy is indicated with postoperative roentgen-ray treatment only in the case in which there is a possibility or probability of peritoneal soiling with malignant cells.

HARVEY B. MATTHEWS.

Irons, W. E., Judd, E. S., Jr., and Dockerty, M. B.: Endometrioma of the Cecum, Proc. Staff Meet. Mayo Clin. 22: 530, 1947.

Endometriosis of the cecum is rather rare. In a review of 2,062 cases of endometriosis at the Mayo Clinic seen from 1923 to 1943, Masson and Cauker reported 14 cases in which

Small doses were given, 15 mmg. daily for one week followed by maintenance doses of 15 mmg. each week.

Alleviation of pain was observed, reduction in size and mobilization of the tumor itself, as well as of the axillary lymph nodes. Microscopic examination revealed no changes whatsoever in the epithelial portion of the tumor which was studied with routine staining methods as well as with such special chromosomic stains as Feulgen and acetic carmine. Instead, the connective tissue was edematous, soft, with increased size of endothelial cells and increased amount of ground substance, a finding which may well account for the mobilization of the tumor, reduction in its size, and alleviation of pain, which symptoms may mislead to the interpretation of an action of the estrogen on the tumor itself. GEMMA BARZILAI.

DeGiorgi, L.: Hydatidiform Mole. Hystopathology of the Placental Site of the Uterus. *Archivio de Ostetricia e Ginecologia* 52: 321, 1947.

At the Lying-in Hospital of Naples, DeGiorgi examined the placental site in four cases of simple hydatidiform mole, for which hysterectomy was performed. The operations were done 2, 19, 37, and 45 days after expulsion of the mole.

Placental site was no different from placental site in a normal pregnancy in Case 1. In the Cases 2, 3, and 4, however, a picture corresponding to Hertig's syncytial endometritis was found. Giant cells, lymphocytic infiltration, marked regressive alteration in the vessels were present. In one case, invasion of the myometrium by endometrial islands was seen, but no invasion by hyperplastic or otherwise malignant trophoblast.

Clinically, these three cases showed uterine subinvolution and stubborn bleeding. The histopathologic picture of the placental site explains those symptoms. In such cases, in spite of the pathologic nonmalignancy of the lesion, hysterectomy is the correct approach, especially after repeated and ineffective curettage. GEMMA BARZILAI.

Crossen, Robert J.: Primary Carcinoma of Bartholin's Gland, *Am. J. Surg.* 75: 597, 1948.

The author reports a case of carcinoma of Bartholin's gland and reviews the literature of the 88 reported primary cases. He discusses the criteria offered by several writers to identify such a primary tumor but does not offer enough details of the presented case to enable the reader to distinguish this lesion from a metastatic corpus adenocarcinoma.

The clinical characteristics of the primary Bartholin gland carcinoma, except for localization, are similar to those of other vulvar tumors. S. B. GUSBERG.

Ayre, J. Ernest: Cervical Cytology in Diagnosis of Early Cancer, *J. A. M. A.* 136: 513, 1948.

The detection of early cancer is always a microscopic procedure. The author proposes an annual cytologic test to detect early carcinoma. In a series of cases of about 115 women who showed cells suggestive of carcinomatous tendencies when the spatula was used, single biopsies failed to reveal any evidence of carcinoma. In those cases which did have a complete conization of the cervix and serial sections of the squamocolumnar junction, 36 preinvasive carcinomas were found and, in a still larger number, cells were found exhibiting the structure by cancer without a lesion large enough or definite enough to be labeled by the pathologist as a preinvasive carcinoma. The author concludes that the described cytologic method gives a sensitive indication of growth changes in the squamous tissues in the region of the junctional area, and it may be possible simply to scrape off a beginning area of growth in tissues, leaving no further evidence to be found in the tissue biopsy. WILLIAM BERMAN.

Gynecology

Defendi, S.: Treatment of Adnexitis by Anesthetic Infiltration of the Hypogastric Sympathetic Chain, *Folia Gynecologica* 43: 3, 1948.

Defendi reports 113 cases of pelvic inflammation treated by infiltration of the hypogastric chain. Acute, subacute, and chronic cases were treated. The procedure was alike

The material was obtained from 21 cases of cancer of the cervix, four cases of cancer of the vagina, five breast cancers, one cancer of the vulva, and two skin cancers.

The above procedures are selective staining methods based on the fact that chromosomes are largely made up of euchromatin which chemically is timonucleinic acid mixed with a globulin-like substance and is different in its staining properties from the heterochromatin which is present in the nucleoli (plasmosomes) and in the cytoplasm, and is chemically made up of a less complex nucleoprotein called ribonucleinic acid mixed with some timonucleinic acid and a large amount of histones. Euchromatin and heterochromatin also differ in their morphologic structure: when fixed and stained, euchromatin appears disposed in tiny regular discs connected by a delicate strand of a material called linin, which has practically no affinity for dyes. Heterochromatin is made up of irregular clumps.

The content of euchromatin and heterochromatin varies in the nucleus according to different phases of its development and life; it also varies according to the nature of the cell. Nucleoli, which are made up of heterochromatin, appear most evident during telephase of mitosis when chromosomes become indistinct and disappear in the prophase when chromosomes became condensed. This has been interpreted as an indication of exchange of material between euchromatin and heterochromatin. Heterochromatin provides the chromomeres with the material they need for reproduction, but this material which is chemically ribonuclein, must be transformed into timonuclein in order to be active. If the capacity to effect this transformation is lost, the cell loses its capacity to reproduce. If in a cell nucleus heterochromatin is prevalent, this means that the normal balance of transformation of ribonucleinic acid into timonucleinic acid is impaired, diminished, or lost. X-ray treatment aims at the destruction of reproductive capacity of cancer cells: *content and disposition of ribonucleinic acid* in the cell are, therefore, a fair indication of the action of x-ray on cancer. By staining cells with selective stains for ribonucleinic acid and timonucleinic acid, the action of x-rays on the cell nucleus can be followed during treatment.

With all three staining methods, Grattarola could demonstrate that in cancer cells at rest timonucleinic acid is predominant and that during irradiation the euchromatin was substituted progressively by the heterochromatin: chromomeres became less and less evident, active nuclei capable of reproduction were transformed into inactive, regressive formations, and this regression could be actually followed, step by step. The importance of this observation can hardly be overestimated.

Barigozzi's method appears to be the simplest and quickest, so that it may become an exceedingly satisfactory means of investigation for the diagnosis of cancer as well as for estimation of the action of x-rays in malignancies.

Stained with Feulgen, timonuclein appears a more or less dark violet, depending on the amount present; ribonuclein is not stained at all; with Unna's method, ribonuclein appears red, timonuclein violet; with Barigozzi's and Cusmano's method morphologic as well as staining differences are apparent. Cells with high content of timonucleinic acid, called "A" cells, show a well-defined nuclear membrane and chromomeres appear as distinct, intensely red granules, while nucleoli appear as light pink vesicular bodies. Cells with high ribonucleinic acid content show an irregular nuclear membrane, a few hyperchromatic clumped granules, and definitely dark-stained nucleoli.

Intermediate types between the two above described extreme types are frequently observed in the first stage of x-ray treatment and are an indication of how x-ray acts on cancer cells. The paper does not mention frequency and appearance of mitosis.

GEMMA BARZILAI.

Sirtori, C., and Grattarola, R.: Estren Effect in Breast Cancer, *Tumori* 21: 319, 1947.

Observations on the effect of estren(dioxydiethylhydrostilbene) on cancer of the breast is reported by Sirtori and Grattarola of the National Cancer Institute in Milano, and an attempt is made to explain clinical signs and symptoms following this treatment on the basis of the variation of the microscopic picture revealed in biopsies taken in sequence.

Items

The Twelfth British Congress of Obstetrics and Gynaecology

To Be Held in the Friends Meeting House, Euston Road,
London, N.W. 1, July 6, 7, and 8, 1949

<i>President:</i> Sir Eardley Holland.	} 58. Queen Anne Street, (Royal College of Obstetricians & Gynaecologists) London, W.1.
<i>Hon. Secretaries:</i> A. Joseph Wrigley.	
Ian Jackson.	

WEDNESDAY, JULY 6.

Morning Session. 10:00 A.M.—(Chairman: The President)

“Modern Caesarean Section.” Introduced by Mr. C. McIntosh Marshall (Liverpool).

Afternoon Session. 2:00 P.M.—(Chairman: Professor Hilda Lloyd)

- (1) Guest Paper, “Endometriosis.” Dr. Joe Meigs (Boston, Mass.).
- (2) “The Methods of Assay and Clinical Significance of Pregnandiol in the Urine.” Introduced by Professor C. F. Marrian (Edinburgh) and Dr. G. I. M. Swyer (London).

8:45 P.M.—Reception by the President and Council of the Royal College of Obstetricians and Gynaecologists at the University of London, Bloomsbury, W.C.1.

THURSDAY, JULY 7.

Morning Session. 10:00 A.M.—

“Essential Hypertension in Pregnancy.” Introduced by Professor George W. Pickering (London) and Professor F. J. Browne (London).

Afternoon Session. 2:00 P.M.—

- (1) “The Management of Pregnancy in Diabetics.” Introduced by Mr. John H. Peel (London) and Dr. G. Douglas Matthew (Edinburgh).
- (2) “Hernia of Pouch of Douglas.” Introduced by Mr. Charles D. Read (London).

8:00-10:30 P.M.—Reception by the President of the Congress at the Zoological Gardens by courtesy of the Council of the Zoological Society of London.

FRIDAY, JULY 8.

Morning Session. 10:00 A.M.—

“Modern Concepts in Diagnosis, Treatment, and Prognosis of Carcinoma of the Uterus.”

1. “The Diagnosis by Vaginal Smear.” Dr. J. E. Ayre (Montreal).
2. “Precancerous Cellular Changes in Carcinoma of the Cervix.” Professor Gilbert I. Strachan (Cardiff).
3. “Prognosis Based on Biopsies.” Mr. A. Glucksmann (Cambridge).
4. “The Operation of Pelvic Exenteration.” Dr. Joe Meigs (Boston, Mass.).

Afternoon Session. 2:00 P.M.—

Discussion on Maternal Mortality. Introduced by Sir William Gilliatt (London).

7:45 P.M.—Congress Banquet in Guildhall

Owing to the difficulties that exist at the present time in arranging hotel accommodation, travel, etc., all those who hope to attend are requested to apply as soon as possible to Ian Jackson, M.R.C.O.G., Hon. Sec., 58. Queen Anne Street (Royal College of Obstetricians and Gynaecologists), London, W.1.

in all cases. Bed rest during the whole procedure, 5 cm. of 1 per cent solution of Novocain were injected at intervals of three to four days, the number varying from six to eight injections.

Acute and subacute cases were cured in about 50 per cent and showed amelioration in 40 per cent of the cases. Chronic cases remained unaffected.

In the acute and subacute cases, spontaneous pain was almost immediately relieved and pain on palpation disappeared after two or three injections. Local signs such as swelling of the tubes and puffiness of the cul-de-sac also disappeared after a few injections, and temperature became normal in most of the cases.

The author considers anesthetic infiltration as worth while trying in the treatment of acute and subacute lesions of the female genitals.

GEMMA BARZILAI.

Menstruation

Markee, J. E.: *Morphological Basis for Menstrual Bleeding*, Bull. New York Acad. Med. p. 253, April, 1948.

An excellent exposition of the morphologic changes in endometrial transplants is presented with their background pattern of hormonal stimulation and their resultant liberation of forces culminating in menstrual bleeding.

The author presents a series of experimental observations in the monkey which indicate the probability that rapid regression is the first of a series of endometrial phenomena leading to menstrual bleeding. Gradual regression induced by gradual decrease in systemic estrogen levels was not accompanied by bleeding; local estrogen application could prevent rapid regression and bleeding in the face of systemic decline in estrogen levels. In all lines of observation, the bleeding phenomenon was constantly preceded by endometrial regression. This regression is thought to be dependent on withdrawal of the growth stimulus of estrogen and progesterone.

The morphologic sequence outlined is that of endometrial regression and thinning with resultant increase in coiling of the coiled arterioles. There is then marked stasis of blood in these vessels and degeneration of the peripheral endometrium; liberation of a toxin from this degenerating tissue will then cause vasoconstriction in these vessels, and weakening of vascular walls results in leakage of blood when vasodilatation ensues. The phase of vasoconstriction is pictured as one which diminishes blood loss.

S. B. GUSBERG.

Miscellaneous

Valle, G.: *Shape of Pelvic Brim in Northern Italian Adult Women*, La Ginecologia 13: 559, 1947.

Valle examined the shape of the pelvic brim in 100 Italian women, including student nurses and housewives, in a small rural town of Northern Italy, using Thoms' technique.

According to Thoms' classification, the percentage of differently shaped pelves rated as follows: dolicepellic 6 per cent, mesatipellic 34 per cent, brachypellic 54 per cent, platypellic 6 per cent.

According to Turner's index, dolicepellic pelves amounted to 21 per cent, mesatipellic to 31 per cent, flat pelves to 48 per cent.

This small series confirms the observation that in Europe the brachypellic type prevails as compared to conditions in the United States where mesatipellic pelves are most frequently found.

Survey of American and continental literature is given, with speculative conclusions about the influence of nutrition on pelvic architecture.

GEMMA BARZILAI.

The second group is that in which feeling of discouragement exists at present, in which we take the position that all we can do is palliate. In Stage III the salvage rate is low. In Stage IV we never have been able to do very much.

There is some justification in the courageous experiment at Memorial Hospital. Today we attempt surgery for these patients, but we must definitely ask ourselves the following questions; First, do we salvage appreciably any from a group of people who previously had no salvage? Second, do we make the patient more uncomfortable than we do with palliative irradiation? Third, is the operative mortality much greater? Fourth, what is the time of palliation?

I note that in Dr. Read's Stage III group, 22 patients, none lived eighteen months. Dr. Healy will tell you that we have had many of these advanced cases, so-called, clinically speaking, who have lived eighteen months or longer.

If we are going to evaluate this courageous experiment, we must ask ourselves these questions.

Since September 15, all patients with cancer of the cervix, whether they have been Stage I, II, III, or IV, who have entered the wards of Memorial Hospital, have been treated surgically. There have been only three cases in which exploratory operation only has been done. They had unusual complications: one had deep metastasis in the liver, which is unusual, the second had complete involvement of the iliac vessels which infiltrated these particular structures, and the third had peripancreatic disease all around the upper abdomen.

Dr. Brunschwig has objected to my term "hemitorsectomy," but I think his term of "devisceration" is just as bad. This operation which includes pelvic lymphadenectomy, removal of uterus, tubes, ovaries, vagina, bladder and rectum, with transplantation of the ureters into the colostomy loop, includes to date 16 cases with 4 deaths, or a 25 per cent over-all mortality. This mortality could be corrected to 12.5 per cent because one patient died on the ninth day after a normal convalescence and autopsy failed to show cause of death; another died of causes unrelated to the operation. But the over-all mortality is still 25 per cent.

I am not speaking critically of this "courageous experiment," and not enough time has elapsed to evaluate it properly, but unless it fulfills the qualifications I have mentioned, it is merely an example of surgical calisthenics. We should not talk about it until enough time has elapsed to evaluate properly its merits or its faults.

There is a very bad feature of this radical surgical procedure. Many aspiring surgeons stand in hero worship of a great surgeon performing these technically remarkable "all American operations." Very few hospitals, even in this city, are equipped to carry on such major surgery. These men, watching this radical procedure and getting the false impression that it is the proved and recognized treatment for carcinoma of the cervix, are going back to their hospitals and attempting to perform the operation without being able even to support the patient properly while she is on the operating table. (Blood transfusions alone often require 6 to 8 units of 500 c.c. each during the operation.)

While I feel it is dangerous teaching before enough time has elapsed to evaluate it properly, I do believe that at Memorial Hospital it is a courageous experiment, worthy of the trial because it is performed on unselected cases and the over-all figure will be an unqualified one.

Foundation Prize Award

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons announces an award of \$200.00 for a thesis based on original work in its field. The manuscript must be presented not later than June 1, 1949.

For further particulars apply to the Secretary, Dr. L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas.

International Congress on Radiology

The Third Congress will be held in Santiago, Chile, from Nov. 11 to 17, 1949. For further information apply to the United States representative, Dr. James T. Case, 55 East Washington Street, Chicago, Ill.

American Board of Obstetrics and Gynecology

The following physicians are to be included in the list of Diplomates certified by this Board:

Bonanno, Peter Joseph, 226 Engle Street, Englewood, New Jersey, born 1909, received M.D. from Georgetown University in 1933.

Heldfond, Alfred John, 5410 Wilshire Blvd., Los Angeles, Calif., born 1911, received M.D. from University of Oregon in 1936.

Steer, Charles Melvin, Harkness Pavilion, 180 Fort Washington Avenue, New York 32, N. Y., born 1913, received M.D. from Columbia University in 1937.

PAUL TITUS, M.D.,
Secretary.

Correction

The Role of Surgery in the Treatment of Carcinoma of the Cervix

In the discussion of a paper with the above title by Dr. Frank R. Smith, published in the December issue of the JOURNAL (pages 1032, 1033), the stenographic notes included inadvertently several statements which require correction. The corrected version is as follows and should be substituted for that previously published. For purposes of continuity the entire discussion by Dr. Smith is presented.

DR. FRANK R. SMITH.—One cannot help but be impressed by the futility of using percentage figures, especially where there is any selected material, for the reason that there is the human equation involved and that differs also where we use a clinical estimation of the stage of the disease, and that is one thing surgery has done in this disease; it has shown us how wrong we have been many times in our clinical estimation of the stage of the disease.

I was interested in Dr. Taylor's estimation of operability. Various surgeons talk about operability, but this differs in different clinics. In this respect I was struck by Bonney's operability of 63 per cent as compared with Dr. Read's of 14 per cent. It would also be of interest to know how many of his patients were irradiated previous to operation and whether they should be classified as to primary operability. At Memorial Hospital in New York we have no "primary" operability; all patients are irradiated before operation.

I desire to submit the following to show the incidence of the various types of carcinoma, taking in Dr. Wm. P. Healy's regime in the first section, from 1922 to 1924. A, or Stage I, shows an increase, due perhaps to increasing publicity and better education of doctors; and B, or Stage II, shows an increase; Stage III diminishes, as would be expected, while Stage IV is about the same. In spite of improvement in material, we find pretty much of a plateau; that is, in recent years there has been a plateau in the results obtained by irradiation. For that reason, we utilized the surgical approach to this disease at Memorial Hospital, to see whether we could improve the cure rate. Now, if we take the two types Dr. Taylor so ably presented, the favorable operability, Stage I and II, and operate on them, giving them irradiation at the same time and postoperative irradiation (preliminary irradiation being given at the present time by the vaginal cone), unless we improve appreciably our over-all statistics in those two groups, the question arises as to whether we are justified in putting the patient through a major surgical procedure as a substitute for the simple insertion of the radium tandem. In other words, if our mortality is greatly increased, and if we fail to improve appreciably our five-year results, are we justified in subjecting the patient to operation?

TABLE I. INCIDENCE

Deliveries, North Carolina Baptist Hospital, January, 1943 to January, 1948	5,180
Cases of toxemia, North Carolina Baptist Hospital, 1943 to 1948	142
Cases of renal suppression, North Carolina Baptist Hospital, 1943 to 1948	7
University of Virginia (Dr. Norman Thornton)	1
High Point Memorial (Dr. Thomas Tyson)	1
Total cases of renal suppression	9

From Jan. 1, 1943, to Jan. 1, 1948, there were a total of 5,180 deliveries in the North Carolina Baptist Hospital. Among these, there were 142 cases diagnosed as toxemia of pregnancy; and, in this group, seven exhibited renal suppression. Of the seven patients, two had relatively mild forms of toxemia with premature separation of the placenta. The remaining five exhibited severe forms of toxemia. *Comment:* These figures should not be considered of statistical value since the shortage of personnel during the war years made accurate cross indexing impossible. No attempt has been made to group the toxemias according to the American Committee of Maternal Welfare classification² since many records did not contain sufficient information.

We have reason, however, to believe the incidence is much greater than is suspected. For instance, when this paper was in preparation, three cases from other hospitals came to our attention; two of which are referred to in this article. The other will be reported later by the attending physician. Three other cases which occurred in Winston-Salem were likewise brought to our attention.

Etiology

The etiology of this syndrome is as yet obscure although certain encouraging leads have been discovered. Lucke³ recently studied a series of 538 fatal cases from a clinicopathologic viewpoint. He concludes that a wide variety of etiologic agents produce similar renal lesions and that "it is appropriate to designate all cases exhibiting these renal disturbances, no matter what their etiologic background, by a single term." He designates the pathologic picture as "lower nephron nephrosis." Among the various causes of this renal lesion, he includes the following:

We are particularly interested in the last four etiologic agents.

TABLE II. ETIOLOGY

- | | |
|-----|-----------------------------------|
| 1. | Crush syndrome |
| 2. | Thermal burns |
| 3. | Heat stroke |
| 4. | Blackwater fever |
| 5. | Chemical poisoning or sensitivity |
| 6. | Alkalosis |
| 7. | Hemolytic transfusion reactions |
| 8. | Nontraumatic muscular ischemia |
| 9. | Toxemia of pregnancy |
| 10. | Uteroplacental damage |

Pathology

The pathologic picture of lower nephron nephrosis depends upon the duration of the process as well as the severity of the original insult. Grossly, the kidneys are pale and swollen and the capsule strips readily. The cortex is considerably widened and pale in contrast to the medulla which is a dusky

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South Atlantic Association of Obstetricians and Gynecologists

*Transactions of the Tenth Annual Meeting,
February 12 to 14, 1948, at Augusta, Georgia*

OLIGURIA AND ANURIA IN TOXEMIAS OF PREGNANCY*

CHARLES H. MAUZY, M.D., AND JAMES F. DONNELLY, M.D.,
WINSTON-SALEM, N. C.

(From the Department of Obstetrics and Gynecology, Bowman Gray School of Medicine)

DEPRESSION of renal secretion constitutes one of the gravest complications of pregnancy. Although it may be due to a variety of pathologic lesions, this discussion will be limited to the syndrome of decreased renal output associated with the various types of toxemia. We will present and discuss nine cases which have come to our attention during the past five years, with the hope of emphasizing the importance of this disorder and its proper management.

A variety of terms have been utilized to describe the degree of renal suppression. According to Dieckmann,¹ anuria is defined as the total absence of any urinary secretion for a period of twelve hours or longer. Oliguria means a urinary output of 600 c.c. per twenty-four hours or less in the presence of an adequate intake and no other source of fluid loss. Other evidence of renal deficiency may be manifested by hematuria, proteinuria, abnormal formed elements in the urine, and general metabolic disturbances.

Incidence

The over-all importance of any problem is related to the frequency of its occurrence and its seriousness. Just how often renal suppression associated with toxemia occurs cannot be determined from the literature.

*Read at the Tenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Augusta, Ga., Feb. 12 to 14, 1948.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

In the cases of transfusion reaction, crush syndrome, and premature separation of the placenta, the source of the injurious material is readily explained. However, in toxemias, uncomplicated by premature separation, the noxious agent is more difficult to discover. One might postulate that toxemia is complicated by tissue destruction, as evidenced by elevated uric acid levels.⁵ The diagram below is a simple illustration of the probable pathogenesis of lower nephron nephrosis (Fig. 1).

PATHOGENESIS OF LOWER NEPHRON NEPHROSIS

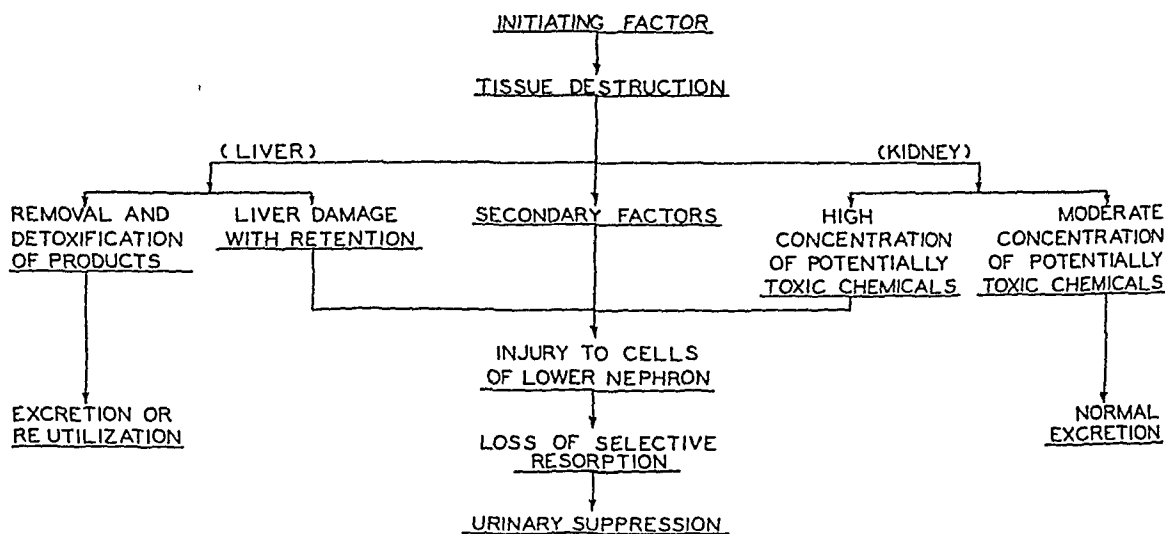


Fig. 1.

Case Reports

With these preliminary remarks, we would like to present the following cases.

CASE 1. Mrs. M. C. P., NCBH No. 47786. A 42-year-old, married, white, gravida vi, para iv, abortus i, was admitted to the North Carolina Baptist Hospital on Jan. 13, 1946. Her calculated date of confinement was March, 1946. The patient had received no prenatal care. Five hours prior to admission, she began to bleed moderately from the vagina and to have pain over the entire abdomen.

Examination on admission showed her temperature to be 98° F., pulse 100, respiration 24, and blood pressure 120/90. The patient was a middle-aged woman who appeared anemic and in acute distress. The uterus was approximately four fingerbreadths above the umbilicus, quite firm and tender, and did not relax. No fetal heartbeat was present. She had a one plus pitting edema of the ankles.

She was immediately cross matched, and a sterile pelvic examination revealed the cervix to be 2 cm. dilated. No placenta could be palpated, and a breech presentation was noted. Membranes were ruptured and the patient received 500 c.c. of whole blood without reaction. At the time of pelvic examination, she was catheterized and 100 c.c. of clear, yellow urine were obtained with the specific gravity of 1.017, no albumin or sugar. Microscopic examination showed 2 to 4 white blood cells, 1 to 3 red blood cells, and no casts. Her hemoglobin was 11.5 Gm. with 4.32 million red blood cells.

Seven hours after the membranes were ruptured, the patient spontaneously delivered a 3 pound, 14 ounce stillborn male infant. The third stage was uncomplicated. She was

red. Microscopically, there is a varying degree of necrosis of the lower nephron with relatively slight damage to the other renal structures. The interstitial tissue is edematous and shows moderate cellular infiltration. Examination of the tubules reveals a number of heme casts present. There may be evidence of vascular thrombosis in some areas of the kidney. The glomerular vessels are singularly free of red cells. Little or no pathology is found elsewhere in the body.

Pathogenesis

The pathogenesis of this disorder is not completely understood. Many explanations have been offered but none have been accepted unequivocally. Very extensive studies on the crush syndrome during the war, however, have elucidated many of the features of the process. The present concept is that cellular destruction by one of the etiologic agents indicated in Table II releases a group of chemicals into the blood stream which, under the proper conditions, causes renal damage. So far, the following chemical substances have produced injury to the renal tissue in experimental animals.

TABLE III. CHEMICAL SUBSTANCES POTENTIALLY TOXIC TO KIDNEY

- | | |
|-----|------------------------|
| 1. | Hemoglobin |
| 2. | Myoglobin |
| 3. | Hematin |
| 4. | Methemalbumin |
| 5. | Sulfhemoglobin |
| 6. | Metmyoglobin |
| 7. | Trypsin |
| 8. | Adenosine triphosphate |
| 9. | Creatine |
| 10. | Potassium |
| 11. | Uric acid |

It is probable that two organs are primarily involved: the liver and the kidney. In the absence of secondary factors, the toxic products are handled without difficulty by the liver and kidney. Normally, the liver removes or detoxifies these chemicals with the excretion of harmless products or the reutilization of certain other products. In the case of the kidney, there is an increased concentration of these products which, in the absence of secondary factors, are excreted without suppression of urinary output.

In the abnormal state, however, the process varies in that some liver damage is present which leads to the failure of removal and detoxification of the products, and their concentration is increased in the blood stream. This leads to an abnormal concentration of these chemicals in the kidney. At this point, the secondary factors, such as decreased blood flow from vasoconstriction or reduced blood volume and acidosis, enter the picture. This combination leads to vasoconstriction and further reduction of the blood flow due to direct action of the chemical substances. In addition, there is actual chemical injury to the tubular cells. These factors acting together cause necrosis of the lower tubular cells. The selective resorptive power of the tubular cells, which maintain the proper balance of water and electrolytes in the body, is now lost. As a consequence of this inability, the larger molecules of the products of tissue destruction become concentrated and precipitate. These precipitated substances then cause further injury to the tubular cells. The diminution of urine, as stated by Bywaters and Dible,¹ "is now due to excessive but unselective reabsorption of the glomerular filtrate through the tubules—in other words, leakage back into the blood stream."

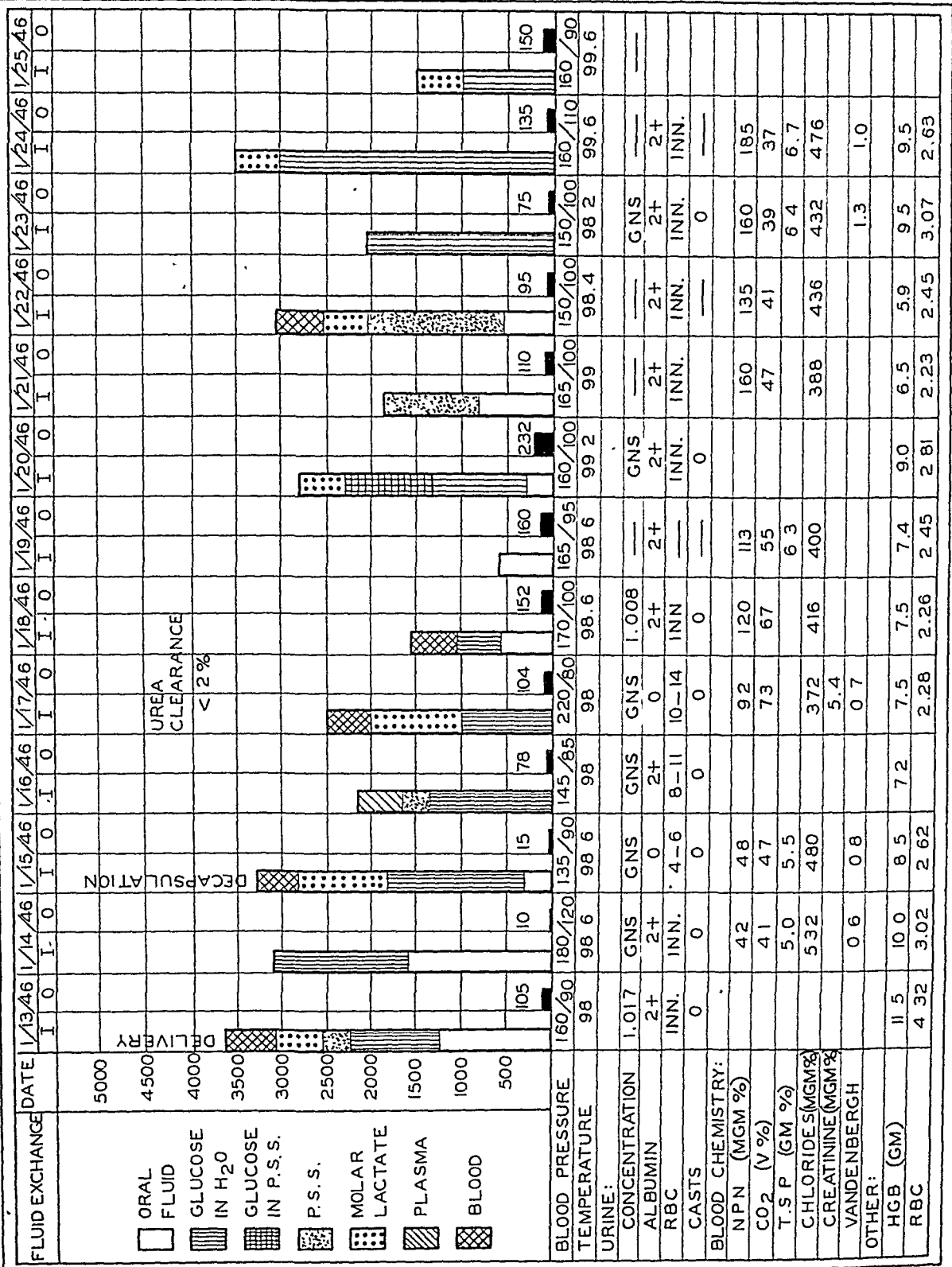


Fig. 2.—Case 1.

catheterized at the time of delivery and only 5 c.c. of dark, bloody urine were obtained. This urine had a two plus albumin and innumerable red blood cells with no casts or hematin crystals. The patient's blood pressure remained around 150/100. Eight hours after delivery this dropped to 100/70 but, two hours later, was fairly well established at 120/80.

Seven hours after the delivery, only 5 c.c. of a dark brownish urine was obtained. The patient had received a total of 4,000 c.c. of fluids intravenously since admission. During the next 18 hours, no urine was obtained. At 10 P.M. on Jan. 14, 5 c.c. of urine which was grossly bloody were obtained. The patient developed generalized edema but repeated examinations of her lungs revealed them to be clear. The patient was digitalized and received 2,000 to 3,000 c.c. of fluids daily, 500 of which consisted of 1/6 per cent molar lactate.

On January 15, her urine was still scanty, with a total of only 12 c.c. since the time of her delivery. A diagnosis of bilateral cortical necrosis of the kidney was made and a segmental block of sympathetic innervation with spinal anesthesia was carried out but failed to benefit the patient. Following this, the right kidney was decapsulated and a biopsy of the kidney was taken.

The pathologic diagnosis on the biopsy of the kidney was cortical necrosis. The microscopic description is as follows: marked necrosis of the tubules, most marked in the convoluted area. Cell outline remains in some instances, but the epithelium has been reduced to a pinkish granular substance. Interesting changes are also taking place in the capillaries in the form of pinkish, acellular deposits.

On the following day, 78 c.c. of urine was passed. The amount of fluid the patient received daily as well as other pertinent information can be seen in Fig. 2. It is interesting to note that on January 19 the patient received the smallest amount of fluids of her entire course and yet the following day her output reached the highest point it ever attained.

The patient's general condition remained fairly good until January 17, when vomiting began and moist râles were noted at the base of both lungs. She became irrational and on January 19 she was placed in an oxygen tent. From that time on until her death, January 25, her course was downhill with the nonprotein-nitrogen climbing. On the day of her death, moist râles could be heard throughout both lung fields and the patient was expectorating a frothy bloody fluid.

Autopsy performed shortly after death revealed the serous cavities to contain moderate amounts of reddish-yellow fluid. Each kidney weighed 175 Gm., the capsule of the left kidney stripped with ease, revealing an external surface slightly lobulated and of a pale reddish-brown color. Scattered petechial hemorrhages were seen on the surface. On sectioning, the cut surface bulged, the cortex was light, grayish-red containing numerous minute yellow streaks. The usual architecture was noted, and the pyramids were well formed. The capsule of the right kidney had been stripped and the surface in its gross appearance was similar to that of the left.

On microscopic examination, the most striking change was thickening and hyalinization as well as loss of cellular detail of the ascending arteriole at the point of entrance into the glomerulus. There is dilatation of some of the proximal convoluted tubules, a few of which are filled with an eosinophilic, homogeneous acellular material. A minimal necrosis is seen in a few of these tubules. The interstitial tissue of the entire organ appears slightly edematous. There was definite evidence of repair, compared to the picture seen at biopsy.

The remainder of the autopsy revealed only the terminal changes one would expect under the circumstances.

This patient exhibited a fairly typical clinical picture of advanced lower nephron nephrosis following premature separation of the placenta and toxemia. This was confirmed by biopsy of the kidney. Her renal output improved temporarily following renal decapsulation; but, as noted in the chart, her intake was not restricted and the patient died in congestive heart failure. We believe that, if fluids had been restricted, this patient

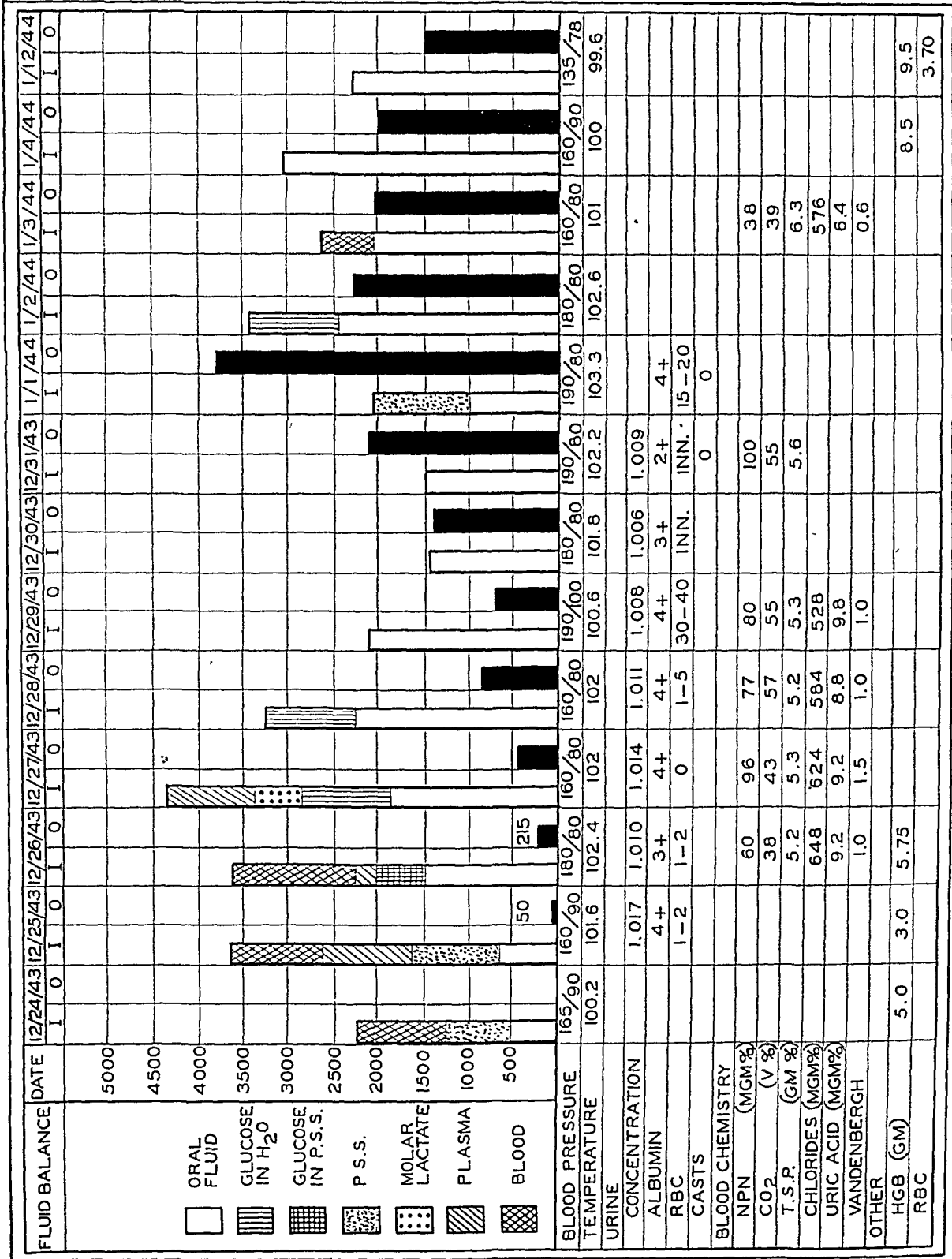


Fig. 4.—Case 3.

might have survived, and certainly her chances would have been greatly improved if peritoneal irrigation had been available. This case also demonstrates the ability of the kidney to regenerate, as shown at the autopsy.

In contrast to this case, we would like to present a case which has been given to us by Dr. Norman Thornton, of the University of Virginia Medical School.

CASE 2.—University of Virginia Hospital No. 233467. This 36-year-old, gravida vii, para iii, abortus iii, was admitted to the University of Virginia Hospital Nov. 28, 1946. Her expected date of confinement was March 2, 1947.

On admission, she was in profound shock with a blood pressure of 80/50. Examination of the abdomen at that time revealed a uterus slightly larger than a six months' gestation. The uterus was hard and tender, some vaginal bleeding was present. Sterile pelvic examination revealed the cervix to be long and closed. The patient received a 1,000 c.c. of whole blood and had a mild reaction with the second 500 c.c. At the time of admission, her hemoglobin was 7.5 Gm. and her red count was 1.8 million. The patient was Rh positive and Type A. She subsequently received a total of six transfusions. All transfusions were Type A and compatibility tests were done on each bottle of blood given.

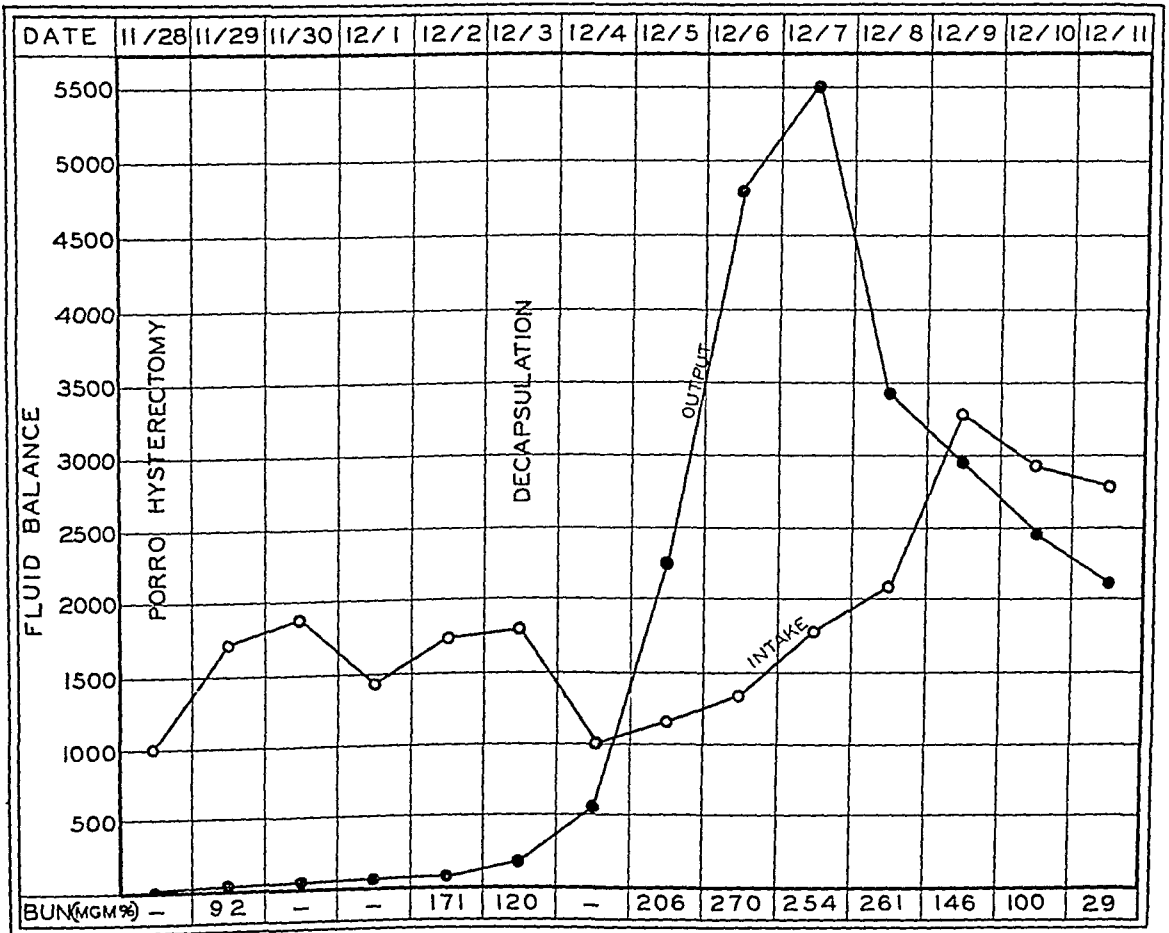


Fig. 3.—Case 2.

Because of the long closed cervix and the persistence of vaginal bleeding, it was thought best to deliver this patient abdominally; and a Porro cesarean section was done. (A typical picture of uterine apoplexy was found at the time of operation.) During the first twenty-four hours after operation, the patient excreted no urine. During the following four days, the urinary output varied between 65 and 90 c.c. daily. The urine specimen

c.c. of serosanguineous fluids were removed from the right chest. The following day another 650 c.c. were removed; and four days later 200 c.c. were removed. The patient had quite a stormy convalescence with a markedly febrile course and received sulfadiazine until the twelfth postoperative day. Numerous transfusions, plasma, and a diet high in proteins and vitamins were also utilized. Blood chemistry gradually returned to normal, and she was discharged on the thirty-second postoperative day with a hemoglobin of 11 Gm. and a trace of albuminuria.

Two things interest us in this case: (1) recovery when the Couvelaire uterus was not removed, and (2) indiscriminate use of intravenous fluids with recovery from oliguria but subsequent cardiac failure and hydrothorax.

We are indebted to Dr. T. D. Tyson, Jr., for permission to use one of his private cases in the following discussion.

CASE 4.—Mrs. Z. W. HP47125. The patient was a 29-year-old primipara with an expected date of confinement March 14, 1947. She was admitted to the High Point Memorial Hospital Jan. 23, 1947, because of hypertension, albuminuria, and excess weight gain. The essential laboratory data are included in Table IV. She went into labor spontaneously on Jan. 29, 1947, delivering a premature stillborn infant at 10:30 P.M. Premature separation of the placenta had been suspected even in the absence of vaginal bleeding and the renal suppression was detected at delivery when only an ounce of urine was obtained, on catheterization (the only output that day).

TABLE IV

DATE	INTAKE C.C.	OUTPUT	SP. GR.	ALBU-MIN	R.B.C.	W.B.C.	CASTS
1/23/47	2,500 oral	1,500 c.c.	1.005	3+	1-2	80-100	0
1/29/47	3,000 plasma 1,000 blood	30 c.c.	1.008	4+	40-60	5-8	5-6
1/30/47	2,000 blood 1,000 5% in H ₂ O	490 c.c.	1.008	2+	70-80	50-60	1-2
2/10/47	2,500 oral	1,500 c.c.	1.008	0	1-2	0	0

Postpartum hemorrhage followed and persisted in spite of oxytocics, uterine packing, and adequate replacement of blood. It was necessary to do a hysterectomy to control the bleeding. Shock was mild. From 10:30 P.M., January 29, to 7:30 P.M. the following day, only 120 c.c. of urine were excreted in spite of an intake of 7,000 c.c. during this period.

The microscopic findings in the urine definitely indicated renal pathology of a nature not seen in uncomplicated dehydration. There is, of course, the possibility that in this case, the renal shutdown was secondary to a transfusion reaction. There was no indication of any systemic reaction, no hematin crystals in the urine, and the recovery was most rapid for such an accident. The blood, on rechecking, was found to be compatible. We, therefore, feel that this patient had premature separation of the placenta with extravasation of the blood into the myometrium leading eventually, with the shock, to renal suppression. The subsequent hysterectomy may have removed the source of the chemical toxins, thus assisting in the recovery of the patient.

CASE 5.—Mrs. M. S. H., NCBH No. 50536. This patient was a 30-year-old primipara referred to the North Carolina Baptist Hospital on April 7, 1946, with the chief complaint of edema, albuminuria, and high blood pressure. Her expected date of confinement was June 5, 1946. In January, 1946, she was seen by her family physician because of swelling of the legs. The edema became worse in February. She was referred to a local hospital. At that time, she had edema of the entire body with a one plus albuminuria. The blood pressure varied between 160/100 to 180/120. She was placed on a salt-free diet, bed rest, Nembutal sedation, intravenous and oral fluids to 2,500 c.c. daily. She failed to respond to this therapy and was sent to the North Carolina Baptist Hospital for further treatment.

on the day following the operation showed a one plus albuminuria and numerous fragmented red blood cells. Because of the oliguria and mounting blood urea nitrogen, a bilateral renal decapsulation was done on the fifth postoperative day. Following this procedure, the patient began to excrete urine; and on the first postoperative day, she passed a total of 635 c.c. On the second day, a total of 2,250 c.c. was voided. She subsequently went on to recovery. Fig. 3 shows the intake and output as well as the blood urea levels.

Biopsy Report.—The outstanding finding in this case is the presence of hemoglobin casts within the lower portions of the nephron. In these areas there is atrophy of the tubules of varying degrees. The interstitial tissue in the immediate vicinity is edematous and is infiltrated with mononuclear cells. The upper portions of the nephrons are dilated, and in some instances show minimal atrophy. Focal areas of scarring and capsular thickening are noted. The findings in this material are compatible with a lower nephron nephrosis and are of the type that has been described in "transfusion kidneys."

This patient showed a remarkable recovery following renal decapsulation. Whether her renal lesion was due to the transfusion reaction or premature separation is open to debate. The shock, premature separation, and transfusion reaction provide an excellent background for lower nephron nephrosis. The removal of the uterus should have been followed by some improvement since the source of the chemical toxins was removed. In all probability, however, the process was sufficiently advanced that hysterectomy offered little benefit to the patient. It is also of interest to note that her fluids were restricted.

CASE 3.—Mrs. B. A. C., NCBH No. 24129. The patient was a 25-year-old, white, gravida iv, para i, admitted to the North Carolina Baptist Hospital on Dec. 24, 1943. The calculated date of confinement was Feb. 20, 1944. The patient had made two visits to our prenatal clinic. She had gained 24 pounds in weight, blood pressure 142/80, occasional severe headaches. A salt-free diet and magnesium sulfate by mouth were prescribed, and she was sent home. At 8 A.M. on the day of admission, she began having labor pains and soon began to bleed profusely. She was admitted to the hospital at 4 P.M. with only slight external bleeding.

Examination at this time revealed an acutely ill, pale, quiet woman. The uterus was quite firm and tender. No fetal heartbeat was present. No vaginal examination was made at this time, but a rectal examination revealed the presenting part to be high, and the cervix to be soft and 2 cm. dilated. At the time of admission, the patient's temperature was 100.2° F., pulse 140, respiration 32, blood pressure 165/80, and hemoglobin 4 Gm.

The diagnosis of premature separation of the placenta was made. The patient received 1,000 c.c. of whole blood. Because of multiparity with a favorable cervix and the fact that the patient tolerated the blood loss well, conservative measures consisting of constant observation and Pituitrin stimulation with two minims every 30 minutes for four doses were decided upon in anticipation of a vaginal delivery. The patient had no labor pains following this but continued to have some slight vaginal bleeding. The following morning, the hemoglobin was 3 Gm. Therefore, delivery was effected by cesarean section eighteen hours after admission. A stillborn male infant was delivered. A huge blood clot was found behind the placenta. Blood had infiltrated the uterine wall and broad ligaments, but the uterus contracted following the delivery of the fetus and placenta and was closed in the usual manner.

The patient received 500 c.c. of blood prior to operation and 500 c.c. of plasma during the operative procedure. She was catheterized at 9 P.M. on the 25th, 29 hours after admission, and only 50 c.c. of urine was obtained. The patient had received a total of 5,800 c.c. of fluids since admission. This urine specimen showed a four plus albumin and only an occasional red blood cell. In the next nine hours, only 40 c.c. of urine was obtained and fifteen hours later, 175 c.c. The amount of fluids and the quantity with the output may be seen in Fig. 4.

The patient received large amounts of fluids daily, although she was described as being quite edematous on her first postoperative day. Definite signs of pulmonary edema were observed on the twenty-seventh and the patient was digitalized on the twenty-eighth. The patient was desperately ill on the thirtieth and thirty-first of December; and on January 1, 700

began to put out clear urine in rather large amounts (a total of 200 c.c. accumulating in one hour). The total output up to this point had been only 400 c.c. On her third day, the blood pressure was noted to be dropping, her treatment with sedation and hypertonic glucose solution was continued. There were râles at the bases of both lungs, and the patient began to complain of severe epigastric pain. The situation was complicated by marked abdominal distention. On her fourth day, she began to complain of pains in the lower part of her back, and was considered to be in labor. The labor progressed rapidly, lasting a total of four hours, terminating in delivery of a 3 pound, stillborn female infant. The third stage was uncomplicated.

Following delivery, the patient's blood pressure ranged from 155/100 to 150/90. She felt better and appeared to be improved. Her urinary output rapidly rose, and her blood pressure fell to normal.

Although no accurate record of this patient's intake and output is available prior to her admission to the North Carolina Baptist Hospital, we are certain that her intake was sufficient to produce an adequate output. We feel, therefore, that the low renal output for the first forty-eight hours, the laboratory findings, and the increasing edema indicated renal suppression. Following fetal death, immediate recovery ensued, clearly indicating that the renal damage was of the reversible type. Complete recovery was proved by repeated urea clearance studies over a period of one year:

April 8, 1946	27 per cent average normal function
April 15, 1946	40 per cent average normal function
Dec. 2, 1946	83 per cent average normal function
April 2, 1947	125 per cent average normal function

CASE 6.—Mrs. L. S. M., NCBH No. 47579. A 39-year-old gravida ii, para i, was admitted to the North Carolina Baptist Hospital Jan. 7, 1946, with an expected date of confinement April 23, 1946. Since the onset of her pregnancy, she had been seen regularly by her local physician who stated that she had a normal blood pressure and negative urine specimens. She was picked up in the hospital corridor, after having fainted. She gave a history of severe headaches, dizzy spells, and spots before the eyes for seven days before admission.

On admission, her temperature was 98.6° F., pulse 92, respiration 20, and blood pressure 170/90. She was a well-developed and nourished woman who showed a slight amount of generalized edema. The heart and lungs were negative. The abdomen was gravid with the fundus measuring 18 cm. She was placed on bed rest, salt-free, high-protein diet and phenobarbital sedation. Her blood pressure fell to 130/80 and remained there. She was discharged after eleven days.

She was readmitted on Feb. 7, 1946, because of a blood pressure that was 190/110 and a two plus albuminuria. Examination, with the exception of the blood pressure, was essentially unchanged. She was placed on the routine pre-eclamptic regime. On Feb. 10, she complained of blindness, nausea and vomiting, and examination revealed her blood pressure to be 210/115. There was marked spasm of the retinal vessels and some blurring of both discs. Sodium Amytal was given as a sedative, and a retention catheter was inserted into the bladder. Throughout the day, there was only a scanty reddish-brown output of urine.

On February 11, her blood pressure came down to 150/100. During a twelve-hour period on the eleventh, the patient excreted only 60 c.c. of urine. Intake, output, blood chemistry, urine, etc., may be observed in Fig. 6. On the following day, there was a definite increase in the urinary output. Hypertonic glucose solutions and sedation were continued.

On the afternoon of February 12, a Braxton Hicks version was carried out, and two hours later the patient was delivered of a 2 pound, 3 ounce stillborn male infant. The third stage was uneventful. Her intake on that day was 180 c.c. of 50 per cent glucose, due largely to the fact that no plan of therapy had been devised, and her intake was almost completely overlooked. Following delivery, her blood pressure ranged between 130 and 140 over 98 and 102. On February 13, she was given hypertonic glucose, both 50 and 20 per cent, and she began to pass large amounts of urine, 800 c.c. in one two-hour period (Fig. 6).

On admission, her temperature was 100.8° F., pulse 100, respirations 20, blood pressure 180/110. There was a three plus albuminuria. The patient was well developed, with generalized edema. The heart and lungs were normal. Ophthalmoscopic examination revealed some blurring of the right disc, and vasospasm of the retinal vessels. The abdomen was gravid with a one plus edema of the abdominal wall. The uterus was enlarged to the level of the umbilicus and a fetal heartbeat was present in the right lower quadrant. Rectal examination revealed marked edema of the labia, vertex presentation, station plus two with the cervix not effaced or dilated. The essential laboratory and clinical data are recorded in Fig. 5.

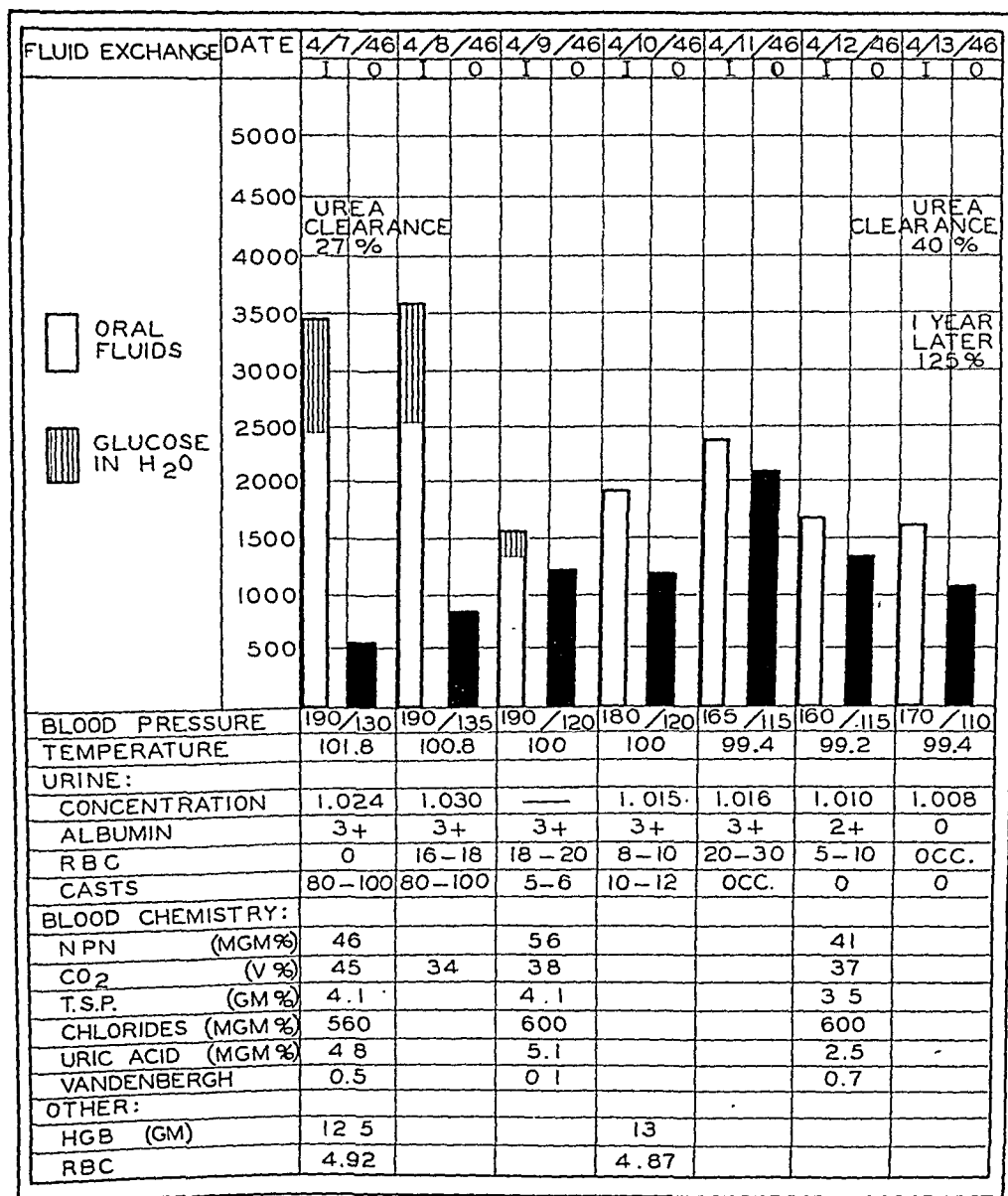


Fig. 5.—Case 5.

The patient was placed on sedation and a high-protein, low-salt diet. In addition, 1,000 c.c. of 20 per cent glucose in water were administered slowly by the vein. The patient developed more edema, became comatose, and distended. The blood pressure ranged from 180 to 190 over 120 to 130. On the second hospital day, the fetal heart sounds disappeared and the urine became grossly bloody. A rectal examination revealed the cervix to be completely effaced, dilated 1.5 cm., and with the head at a station minus one. At 10:30 P.M., the patient

albuminuria ranging from one to two plus. Her intake and output remained normal. Blood chemistries on October 24 were normal with the exception of the uric acid which was 19.2 mg. per cent.

On November 5, she developed a three plus albuminuria with no change in her blood pressure. On the morning of November 8, a urine specimen revealed a specific gravity of 1.010, three plus albuminuria, many finely granular casts. In the afternoon, another specimen revealed a specific gravity of 1.009 with a three plus albuminuria and 20 to 30 red cells with many casts. A cesarean section was decided upon since the cervix was unfavorable for a vaginal delivery. A grossly bloody urine specimen of 10 c.c. was secured just prior to operation. This was loaded with red cells and contained many casts. The delivery was uneventful. Two viable fetuses were delivered and a third macerated stillborn fetus was found. There was at no time any suppression of the urinary output. The red cells, casts, and albuminuria gradually disappeared. With the exception of her uric acid, the blood chemical studies have all been within normal limits.

This patient is of interest because she rapidly developed evidence of severe renal injury. As soon as it became evident that the lesion was progressing, the pregnancy was terminated by operative delivery and prompt recovery occurred. The delivery, like the fetal death in Case 5, probably eliminated the source of the nephro-toxin. In this case, the renal lesion was detected at the first sign of progression.

CASE 8.—Mrs. C. H. W., NCBH No. 49887. The patient was a 20-year-old, white primipara admitted on March 19, 1946, having had three convulsions prior to admission. Her expected date of confinement was March 22, 1946. This patient had received no prenatal care.

Her blood pressure on admission was 170/120 and the urine contained a four plus albumin, hyaline casts, 6 to 8 red blood cells, and 26 to 28 white blood cells. The uterus was gravid and appeared to be at term with a vertex presentation. The fetal heartbeat was heard in the right lower quadrant. The patient was quite irrational and disoriented, and was treated conservatively with intravenous fluids, sedation, and rest.

On the day of admission, her intake was 980 c.c. and her output 270 c.c. On the second day, her intake was 3,230 c.c. and output 1,410 c.c. On the third day, the patient began to show definite signs of oliguria and in a period of eight hours, passed only 50 c.c. of dark bloody urine after having received approximately 1,500 c.c. of 10 per cent glucose in water several hours prior to this. Her blood pressure continued to rise in spite of conservative treatment and because of this, plus the urinary findings, a low corporeal cesarean section was performed and a 6 pound, 13 ounce living male infant was delivered. Four hours after delivery, the output of urine became adequate and remained good. The patient was discharged on April 10, her twenty-third hospital day.

This patient was a severe eclamptic and did not improve under conservative treatment. She was delivered by cesarean section because of rising blood pressure and oliguria with immediate recovery from oliguria after the delivery. Had the delivery been delayed, the kidney lesion might have become irreversible.

CASE 9.—Mrs. D. F. F., NCBH No. 60208. This patient was a 24-year-old primipara who was admitted to the North Carolina Baptist Hospital on Dec. 16, 1946, because of severe hypertension. Her calculated date of confinement was Jan. 1, 1947. She had developed generalized edema and marked weight gain during the past three weeks.

Examination on admission revealed a blood pressure of 170/100 and a three plus pitting edema of the extremities. The abdomen was gravid near term, presentation vertex. The urine contained a two plus albumin and occasional granular cast. Her blood chemistry showed a uric acid of 5.8 mg. per cent, carbon dioxide combining power 43 volumes per cent, non-protein nitrogen 33 mg. per cent. Her weight was 238 pounds.

The patient was placed on conservative treatment consisting of sedation and salt free diet. During the first week with this conservative treatment, her blood pressure became fairly well established at 140/100 and the albuminuria decreased. The intake and output during

She returned on April 10 for a follow-up examination. Her blood pressure was 180/100. A tubal ligation was carried out on June 17, at which time she still exhibited a mild hypertension.

This patient appears to represent a case of essential hypertension. While under medical treatment, the urine became scanty and reddish-brown in color, and a radical termination of the delivery was selected. The outcome would seem to support the decision.

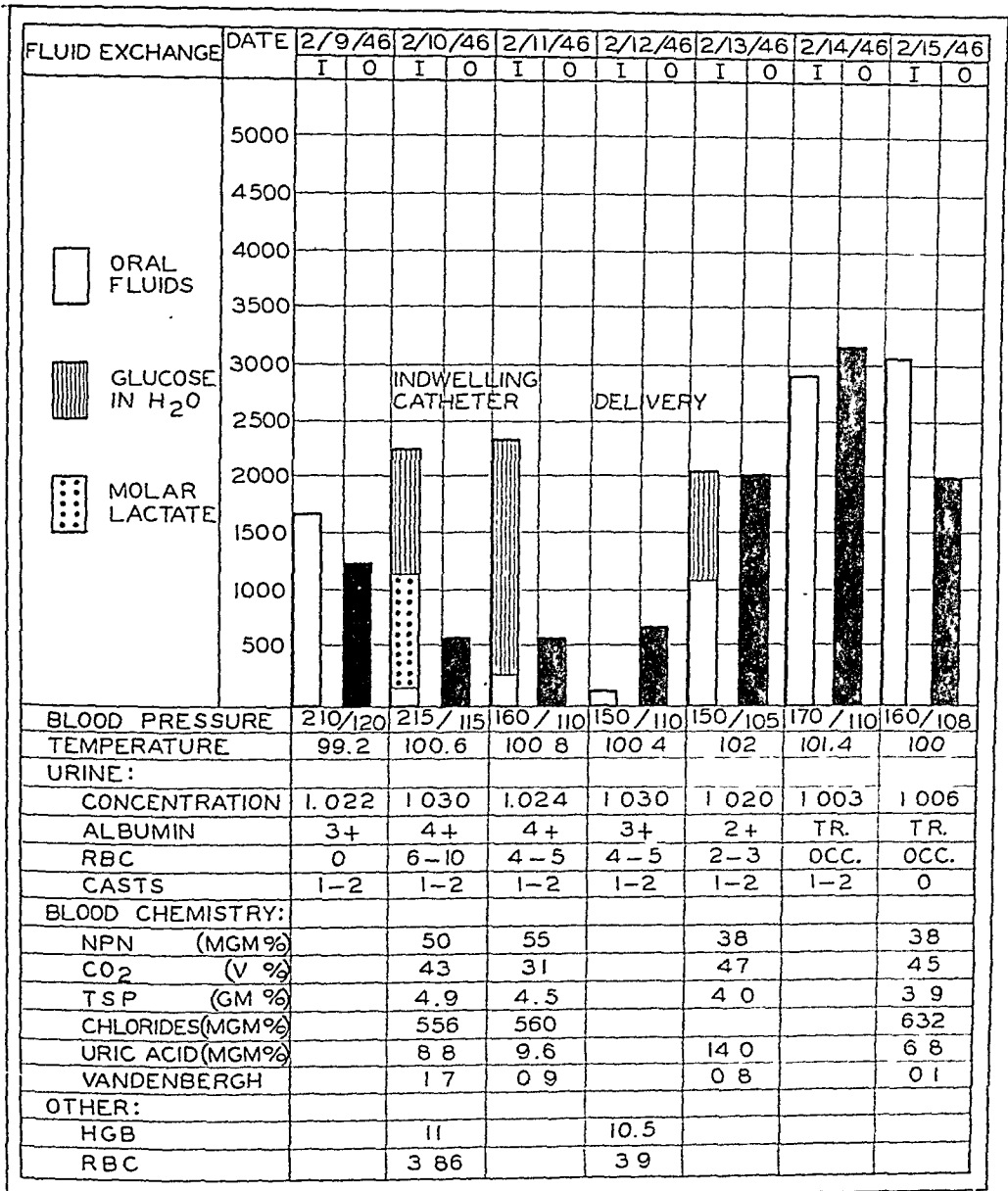


Fig. 6.—Case 6.

CASE 7.—Mrs. C. L. S., NCBH No. 49439. This patient was a 35-year-old primigravida admitted on Oct. 15, 1946, with an expected date of confinement on Nov. 27, 1946. Twin pregnancy was diagnosed Aug. 9, 1946. She was referred to this hospital for further prenatal care and delivery. On October 15, her blood pressure was found to be 150/90, and there was a heavy trace of albumin in the urine.

She was admitted to the hospital the following day. Her blood pressure remained around 120/90 with occasional readings going as high as 150/100. She had a persistent

Hypertonic glucose may be of value prior to the onset of oliguria but fails once real anuria has set in. If given before tubular failure, hypertonic solution may result in increased blood volume and increased renal blood flow. After this point, it is of no benefit in the production of increased renal blood flow. However, carbohydrates protect liver function and should be continued in restricted amounts regardless of the renal output.

Ureteral irrigation has been advocated in the past, but this practice is of questionable value. However, it is essential to make a thorough study of the lower urinary tract in order to exclude an obstruction as cause of anuria.

Renal decapsulation has many enthusiastic supporters. Peters⁸ lays great stress on increased intrarenal pressure with reduced renal blood flow as a cause of anuria and states that this is relieved by freeing the kidney capsule. Perhaps it is not only the release of pressure but also an interruption of the vasoconstrictive action, due to the removal of sympathetic nerves between the capsule and cortex, that increases renal blood flow. Fisher⁹ states that the capsule is a reflex regulating apparatus for blood flow through the kidney and that decapsulation produces a renal sympathectomy. To be of value the procedure should be done early, before the process becomes irreversible.

Peritoneal irrigation was unknown to us at the time of our patient's death but has been used recently in our hospital with dramatic results following a severe blood transfusion reaction. Grossman, Ory, and Willoughby¹⁰ report the recovery of a postpartum woman with anuria and azotemia of eight days' duration by this means. Streat, Korenberg, and Portnuff¹¹ had a similar experience with a postpartum patient who developed a transfusion reaction, and severe anuria. The use of the peritoneal cavity as a substitute for the kidney in the removal of metabolic products offers a new concept in the treatment of anuria and may prove lifesaving to many patients who would previously have succumbed.

Repeated blood chemistry studies must be made on all anuric patients and attempt made to control the blood chemical balance. This is particularly important in those patients who are having peritoneal irrigation.

Routine digitalization of these patients may prevent pulmonary edema and congestive heart failure which is the immediate cause of death in most cases. One must also remember that, even if fluids are restricted, occult accumulation of fluid may occur due to marked tissue destruction and give rise to congestive failure. Other supportive measures such as oxygen are always of value.

Our procedure of treatment on anuria may be summarized as follows: (1) limitation of fluids, (2) maintenance of normal blood chemistry, (3) ureteral irrigation, (4) renal decapsulation, (5) peritoneal irrigation, and (6) supportive measures.

Conclusions

1. Oliguria and anuria present a most serious complication in toxemia of pregnancy. Recent obstetric literature has failed to give this clinical picture its proper recognition.

2. The incidence in our series of toxemia over a five-year period was 5 per cent, with one death.

3. The etiology is still unknown but recent experiences with crush syndrome, transfusion reaction, etc., have yielded much information.

4. Pathology is limited mainly to the lower nephrons although other kidney lesions may be present as the disease progresses. The tubular cells have the power to regenerate after injury.

this time was adequate. On December 24, eight days after admission, her blood pressure was 150/110, and her output was only 250 c.c., in spite of an intake of 2,450 c.c. The following day, her blood pressure was 170/120, urinary output 100 c.c. with an intake of 1,950 c.c. At this time, no fetal heartbeat could be heard. On December 26, labor was induced by artificial rupture of the membranes, and the patient was delivered nine hours later of a 9 pound still-born child under pudendal block by means of low forceps.

Two hours after delivery, the patient developed severe pulmonary edema, and her blood pressure dropped to 120/60. She was treated with phlebotomy, 1,000 c.c. of blood being withdrawn, oxygen, aminophyllin, and digitalis.

On the day of delivery, she had an output of 500 c.c. with an intake of 550 c.c., consisting mainly of hypertonic glucose. The day following delivery, her intake was 4,095 c.c. and output was 1,200 c.c. The latter remained adequate until the time of discharge on January 10. Blood pressure on discharge was 120/70. The only abnormal blood chemistry finding was a uric acid of 11.5 mg. per cent.

This case would seem to demonstrate how easily oliguria might arise even with the patient under observation and apparently showing improvement in her toxemia. The drop in blood pressure following delivery may have been due to release of the vasoconstrictor forces. As a consequence, the increased renal blood flow would tend to promote increased renal secretion.

Treatment

It is of prime importance in treating toxemia of pregnancy to watch the intake and output of fluids and maintain a suitable chemical and fluid balance. Should the output of urine, in spite of an adequate intake, descend to oliguric or anuric levels, the uterus should be emptied immediately. Fortunately, in the majority of cases, provided that secondary factors such as hemorrhage, liver damage, trauma from difficult delivery, or sudden fall in blood pressure are absent, the normal physiologic processes will maintain an adequate urinary output.

However, oliguria or anuria persisting after delivery or associated with one or more of the previously mentioned secondary factors is a most serious complication. One is now dealing with a kidney lesion which may be severe or may, if further insulted by too heroic measures, prove irreversible. However, the kidney, like other organs, if given time and proper treatment, may repair the damage and its function be restored to normal.

Treatment must be directed so that the tubular cells have an opportunity to regenerate while maintaining the blood electrolyte balance. Treatment is always controversial when the disease process is not completely understood. We recognize that differences of opinion exist.

Fluids should be restricted to 1,500 c.c. in any twenty-four hour period (including blood, intravenous fluids, and those taken by mouth) unless there are indications for greater amounts, such as blood loss. A kidney that is already swollen and edematous will only become more waterlogged when an attempt is made to break the so-called blockage by forcing fluids. It should be remembered that the mechanism of suppression is not faulty glomerular excretion but rather almost total resorption of fluids from the diseased distal convoluted tubules. Therefore, excessive fluids will be retained until tubular function recovers. Excessive fluids alone are probably the most frequent cause of death in lower nephron nephrosis. Lattimer⁶ had seven cases of anuria which recovered when fluids were restricted to 1,000 to 1,300 c.c. When fluids were forced to 3,500 to 6,000 c.c., 75 per cent of the patients died with frank edema and cardiac failure. Kugel⁷ reports two cases with severe oliguria (carbon tetrachloride poisoning and transfusion reaction) which recovered under a regime that consisted mainly of limiting fluids.

AN EVALUATION OF 354 CONSECUTIVE HYSTERECTOMIES PERFORMED AT THE ORANGE MEMORIAL HOSPITAL*

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(From the Department of Gynecology, Orange Memorial Hospital)

CONSIDERABLE publicity has been given recently to the topic of unnecessary operations. At least two lay publications have sponsored articles quoting prominent surgical authorities and presenting scathing indictments against surgeons in general for their promiscuity in the removal of normal organs. That these charges are true, in isolated instances, no one will deny, but the implication that this deplorable situation is generally prevalent has harmful and dangerous potentialities. Public resentment can conceivably be aroused to the degree that necessary, or even lifesaving, operations may be regarded with an attitude of skepticism, causing undue delay or rejection on the part of the patient. Surgeons have been placed on the defensive by these charges, and we, as gynecologists, must accept our share of the responsibility. Hysterectomy appears to be the operation, in the gynecological field, bearing the brunt of the accusations.

Miller,¹ by questionnaire, has reviewed 246 hysterectomies performed during the first four months of 1945 in ten different hospitals, large and small, in three midwestern states, with a correlation of the symptoms, pelvic findings, and histopathology. His study revealed the startling findings that 30.8 per cent of the organs removed in the series presented no evidence of disease and that in 32.8 per cent the operation was either not indicated or contraindicated. He reaches no definite conclusion in his report, but the inescapable one must be drawn that if his findings represent a cross section of the country as a whole, hysterectomy has attained an unenviable place at the top of the list of unnecessary operations. This offers a challenge to hospital staffs to "look behind the curtain" as Miller suggests, turning on the cold light of scrutiny and taking remedial measures as indicated. This is necessary if we are to retain public confidence and respect.

The present study was undertaken for the purpose of determining the hysterectomy situation at the Orange Memorial Hospital. This hospital is a fully approved 250 bed institution with a well-organized staff and a full-time certified pathologist. It is impossible to make any comparison between this staff and those of the ten hospitals reviewed by Miller, but the fact that all organs removed in those hospitals received a pathologic examination would indicate that they meet at least minimum, or better, requirements. It was hoped that some conclusions could be reached as to whether hysterectomy is an abused operation in the Orange Memorial Hospital, or whether the errors in diagnosis and indications for operations approach that irreducible minimum

*Read at the Tenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Augusta, Georgia, Feb. 12 to 14, 1948.

5. The pathogenesis involves many factors, none of which acting alone seem to be responsible but acting together render the tubular cells susceptible to injury by certain chemical substances.

6. Nine case histories are presented and discussed.

7. It is our opinion that once oliguria or anuria develops the interruption of pregnancy is mandatory.

8. In view of the tubular damage with leakage of the glomerular filtrate into the blood stream, excessive fluids will lead to cardiac decompensation and pulmonary edema with death; therefore, they must be restricted.

9. Renal decapsulation, in our experience, is of questionable value but is a lifesaving procedure in some cases.

10. Peritoneal irrigation is a valuable procedure; serving as an artificial kidney, it removes the waste products during the period of tubular regeneration.

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total operation is in the removal of the diseased cervix. However, since I have personally treated five carcinomas of the cervical stump within the last year, the advantage to me is genuine, and there seems little justification for the experienced operator not to employ the total operation except in difficult cases such as extensive pelvic endometriosis or inflammatory disease, where the safety of the patient might be endangered by the removal of the cervix. I am also sure that the total operation is technically more difficult, and the occasional operator had best confine his hysterectomies to the subtotal type.

The gynecologic staff showed a decided preference over the surgical for the vaginal type, 27 per cent to 7 per cent. However, here again it was found that two of the seven gynecologists did 58 of the 63 vaginal hysterectomies.

There were two deaths in the 354 cases, a mortality rate of 0.7 per cent in the abdominal hysterectomies, or 0.56 per cent in the whole series. Both of these deaths were due to pulmonary emboli, one on the second postoperative day (autopsied), and the other on the eighth day while the patient was in the chair. Both also occurred in the subtotal operations, done by the surgical service. These facts are not considered significant as both deaths were apparently unpreventable.

TABLE III. SYMPTOMS OF PATIENTS

COMPLAINT	NUMBER	PER CENT
Bleeding	148	41.8
Pain, lower abdomen	111	31.3
Dysmenorrhea	73	20.6
Leucorrhea	54	15.3
Backache	50	14.0
Mass, lower abdomen	49	13.8
Secondary symptoms	46	13.0
{ headache		
{ nervousness		
{ fatigue		
{ weakness, etc.		
Urinary symptoms	33	9.3
Bearing down or heavy feeling in the lower abdomen	32	9.0
Prolapse	24	6.8
No symptoms	10	2.8
Dyspareunia	6	1.7
Pregnancy	6	1.7

Table III shows the complaints of the patients at time of examination. Many had multiple symptoms. One hundred forty-eight patients, or 41.8 per cent, complained of abnormal bleeding. This agrees very closely with the figure of 41.4 per cent in Miller's series. Three hundred eight, or 78 per cent, complained of bleeding and/or pain and a mass in the lower abdomen. There is considerable variance in this series in the number of patients who presented no symptoms, 10, or 2.8 per cent, and 43, or 17.4 per cent, in Miller's. I am unable to explain this discrepancy except on the basis of incomplete histories.

In the 354 pelvic examinations (Table IV) fibroids were discovered 205 times, 57.9 per cent. By comparison, Miller found this diagnosis in 31.7 per cent of the cases in his report. The most significant disclosure is the difference between the normal pelvis, reported in these two studies, 2, or 0.6 per cent, in this, and 46, or 18.6 per cent in Miller's. Again, it is difficult to reconcile the fact that normal pelvic findings in the latter group were 30 times greater than in this series. Pregnancy was discovered eight times, and hysterectomy was

which can be attributed to honest, human mistakes in diagnostic skill and surgical judgment. This latter figure is difficult to compute and will vary with individual interpretation.

Material

A personal analysis was made of the hospital case records of 354 consecutive hysterectomized patients between April 5, 1946, and Dec. 17, 1947. The date for the beginning of the study was chosen because it coincided with the return of the pathologist to the hospital after a leave of absence. The hysterectomies were performed by 21 different operators, seven belonging to the gynecologic, and fourteen to the general surgical staff of the hospital. The largest number of operations done by one staff member was 113 and the least one. Fourteen members were responsible for less than ten hysterectomies each. Permission was obtained from all the members concerned in the study for a review of their charts with the knowledge that the findings would be reported.

TABLE I. TYPE AND NUMBER OF HYSTERECTOMIES ACCORDING TO AGE GROUPS

TYPE	UNDER 20	20-29	30-39	40-49	50-59	60-69	70-79	NUMBER
Total		12	44	53	11			120
Subtotal	1	19	70	60	12	1		163
Vaginal		3	18	27	14	6	3	71
Total number	1	34	132	140	37	7	3	354

Table I indicates the number and types of hysterectomies according to age groups. The largest number, 140, (40 per cent) was performed, as might be expected, in the group 40 to 49 years of age. This group also contains the greatest number of the total type, 53, or 44 per cent. Thirty-five hysterectomies, or 10 per cent, in patients under 30 years of age appear high, and deserve the closest scrutiny in the final analysis. Nine of the ten cases in the group 60 to 79 years old are of the vaginal type. This is in accord with the accepted trend of the use of the vaginal route in elderly patients.

TABLE II. TYPE AND NUMBER OF HYSTERECTOMIES ACCORDING TO HOSPITAL SERVICE

TYPE	GYNECOLOGIC SERVICE	PER CENT OF 232	SURGICAL SERVICE	PER CENT OF 122
Total	88	38	32	26
Subtotal	81	35	82	67
Vaginal	63	27	8	7
Total number	232	100	122	100
Per cent of 354	65.5		34.5	

The number and types of hysterectomies according to service in the hospital are listed in Table II. The gynecological service showed a preference for the total operations over the surgical group, 38 per cent to 26 per cent. However, when this was broken down, it was discovered that two gynecologists performed 84 of the 88 total type, and three general surgeons 25 of the 32 totals in that service, or that five operators of the 21 did 90 per cent of the total operations. It is evident that both groups as a whole have not accepted the generally asserted advantage of the complete over the incomplete operation, or else have properly recognized their limitations. I am in complete agreement with Miller that the only advantage of the total over the sub-

TABLE V. PATHOLOGY OF ORGANS REMOVED

FINDING	ABDOMINAL OPERATION	PER CENT OF 283	VAGINAL OPERATION	PER CENT OF 71
Fibroids	180	63.6	25	35.2
Cervicitis	120	42.0	68	95.8
Salpingitis	64	22.6	1	1.4
Ovarian tumors				
Benign	54	19.0	1	1.4
Malignant	4	1.4		
Hyperplasia endometrium	24	8.4	9	12.7
Uteri				
Normal except cervicitis 12	22	7.7		
Normal except pregnancy 6				
Normal 4				
Endometrial polyps	21	7.4	5	7.0
Adenomyosis	20	7.0		10.0
Pregnancy or retained products	15	5.3		
Endometriosis	9	3.2		
Fibrosis uteri	9	3.2	3	4.2
Cervical polyps	5	1.8	3	4.2
Carcinoma corpus	3	1.1	1	1.4
Myosarcoma	2	.8		
Tubal pregnancy	1	.4		
Postpartum uteri				
Hemorrhage	1	.4		
Rupture	1	.4		
Pyometria	1	.4		
Bicornate uterus	1	.4		
Uterus didelphys	1	.4		

There were 15 cases of pregnancy or retained secundines discovered on pathologic examination. These were analyzed and the results are listed in Table VI.

TABLE VI. PREGNANCY OR RETAINED PRODUCTS FOUND ON PATHOLOGIC EXAMINATION—
15 CASES

FINDING		NO. CASES RECOGNIZED	NO. CASES UNRECOGNIZED
Hysterectomy indicated, 9 cases	Sterilization for medical indications with consultation	5	
	Retained secundines with fibroids		3
	Fibroids. 6 months' pregnancy. Hemorrhage. Possible rupture	1	
Hysterectomy not indicated, 6 cases	Normal pregnancy		4
	Pregnancy with fibroids. No consultation	2	
Total number		8	7

Justification of Hysterectomies on Basis of Pathologic Findings

In 237 of the 283 cases of abdominal hysterectomy (83.7 per cent), the pathologic findings confirmed the clinical diagnoses. Removal of the uterus was considered justifiable in all but two of these cases, 235, or 83.3 per cent. In Miller's report, 122 of the 246 cases (49.6 per cent) were confirmed. All of these were considered justifiable. This appears to be a real basis for comparison between the two series. In order not to pad or distort the results, the vaginal hysterectomies (71) are not included in this statistical study, as the indication for operation in this group was primarily prolapse rather than diseased organs. Of the 46 cases in which the clinical diagnosis was not con-

performed for various reasons as shown later. Outside of two of these cases, the two normal pelves, and one case of suspected carcinoma of the cervix, where total hysterectomy was contraindicated, there would appear to be no preoperative diagnosis that did not grossly indicate operation. However, the accuracy of these findings remains to be vouched for.

TABLE IV. PELVIC FINDINGS ON EXAMINATION

FINDING	NUMBER	PER CENT
Fibroids	205	57.9
Cervicitis	106	30.0
Prolapse, uterus	60	17.0
Relaxation, perineum	59	16.7
Cystocele	48	13.8
Salpingitis	32	9.4
Ovarian cysts		
Benign	27	7.6
Malignant	2	.6
Rectocele	23	6.5
Retrodisplacement, uterus	18	5.1
Fibrosis uteri	10	2.8
Pregnancy	8	2.3
Endometriosis	7	1.9
Adenomyosis	6	1.7
Cervical polyps	4	1.1
Abdominal adhesions	3	.9
Pyometria	2	.6
Ruptured uteri	2	.6
Carcinoma, corpus	2	.6
Normal pelvis	2	.6
Carcinoma, cervix	1	.3
Postpartum uterus (hemorrhage)	1	.3
Tubal pregnancy	1	.3
Intestinal obstruction	1	.3
Leucoplakia, cervix	1	.3

The pathologic findings are divided between the organs removed by the abdominal and vaginal routes and are catalogued in Table V. Fibroids were found 205 times in both groups (57.9 per cent). Peculiarly, this was the exact figure in the preoperative findings. I must reluctantly disclaim this as evidence of supernatural diagnosis and regard it as a coincidence. Miller's figures show fibroids present in 43.4 per cent. Since all of these fibroids were undoubtedly not of sufficient size to warrant operation, it was interesting to note that 170, or 83 per cent, had symptoms of abnormal bleeding, and/or abdominal pain and palpable abdominal mass, generally acceptable criteria for hysterectomy. Of the other 35, 12 were removed by vaginal hysterectomy for reason of prolapse, and of the remaining 23 only four were asymptomatic. There were four uteri diagnosed as normal, twelve normal with the exception of chronic cervicitis, and six normal with the exception of pregnancy. In the abdominal cases, chronic cervicitis per se was not recognized as an indication for hysterectomy. This gives a total of 22 cases, or 7 per cent, in which operation was not justified for lack of pathology. In the 71 vaginal hysterectomies, all cases showed prolapse and/or sufficient uterine pathology to justify operation except two, as will be shown in the final summation, where it was felt the operation was ill chosen. If these 69 cases are included in the total series, the incidence of insufficient pathology or relaxation for operation is reduced to 6.8 per cent. Miller's group of 246 cases, including 12 vaginal hysterectomies, showed no pathology or relaxation in 76 instances, or 30.8 per cent.

- CASE 5. Age 27. Dysmenorrhea. No bleeding. Total hysterectomy. Finding, hemorrhagic cyst ovary. Chronic cervicitis.
- CASE 6. Age 25. Abdominal pain. No bleeding. Subtotal hysterectomy. Finding, benign endometrial polyp.
- CASE 7. Age 35. Dysmenorrhea. No bleeding. Subtotal hysterectomy. Finding, hyperplasia endometrium. Chronic cervicitis.
- CASE 8. Age 47. Leucorrhea. No bleeding. Subtotal hysterectomy. Finding, benign endometrial polyp.
- CASE 9. Age 24. Menometrorrhagia. Subtotal hysterectomy. Finding, multiple retention cysts ovaries.
- CASE 10. Age 36. Dysmenorrhea. No bleeding. Total hysterectomy. Finding benign endometrial polyp.

TABLE VIII. FINAL SUMMATION OF ORANGE MEMORIAL'S AND MILLER'S SERIES

	ORANGE MEMORIAL'S SERIES 283 CASES		MILLER'S SERIES 246 CASES	
	NO. CASES	PER CENT	NO. CASES	PER CENT
Patients with no symptoms	10	2.8	43	17.4
Patients with normal pelves	2	.6	46	18.6
No pathology (or relaxation)	16	5.6	76	30.8
Clinical diagnosis confirmed by pathologist	237	83.7	122	49.6
Clinical diagnosis not confirmed by pathologist	46	16.3	124	50.4
Hysterectomy justified	251	89.0	165	67.0
Hysterectomy unjustified	32	11.0	81	32.8

For a summary of the comparison between the justified and unjustified 283 abdominal (1 vaginal) hysterectomies in this series, and the 246 (including 12 vaginal) in Miller's, attention is again directed to Table VII. The final summation of the two series can be seen at a glance in Table VIII. The main point of interest is that in Miller's study the clinical diagnoses were not confirmed by the pathologist in approximately three times as many cases as in the Orange Memorial Hospital's and the hysterectomy was judged unjustified in about the same ratio. This should emphasize the role of the pathologist as the final arbiter in the justification for any operation where the removal of organs is involved.

Misuse of Type of Hysterectomy

In a study of this nature, attention should be directed to the cases where hysterectomy was apparently indicated, but the interest of the patient would have been better served by the use of a different type of hysterectomy than the one employed. Three cases, of the 354 reviewed, were considered to fall within this classification and are briefly evaluated as follows.

- CASE 1. Age 53. Irregular bleeding. Vaginal hysterectomy. Finding, adenocarcinoma of the corpus. A preliminary curettage was indicated, followed by radium, and later, total hysterectomy.
- CASE 2. Age 63. Irregular bleeding. Subtotal hysterectomy. Finding, adenocarcinoma of corpus. The same procedure should have been employed as in Case 1.
- CASE 3. Age 36. Prolapse. Total hysterectomy with no vaginal repair. Patient would have been better served by vaginal hysterectomy and posterior colporrhaphy.

Thus, it will be seen that there was a misuse of the type of hysterectomy in 3 of 354 cases, or 0.80 per cent.

firmed by the pathologist, the operation was considered justifiable in 16, or 5.7 per cent. Miller's figure in this category is 43 cases (17.4 per cent).

TABLE VII. SUMMARY OF JUSTIFIED AND UNJUSTIFIED HYSTERECTOMIES

	ORANGE MEMORIAL'S SERIES 283 CASES		MILLER'S SERIES 246 CASES	
	NO. CASES	PER CENT	NO. CASES	PER CENT
<i>Hysterectomy Justified</i>				
Clinical diagnosis confirmed by pathologist	235	83.3	122	49.6
Clinical diagnosis not confirmed by pathologist	16	5.7	43	17.4
Total	251	89.0	165	67.0
<i>Hysterectomy Not Justified</i>				
Minimal symptoms and pathology	2	.7		
Clinical diagnosis confirmed by pathologist				
Clinical diagnosis not confirmed by pathologist	8	2.7		
No histopathology (or relaxation)	4	1.4	76	30.8
No histopathology except cervicitis	12	4.2		
Diagnosis contraindication to operation (pregnancy or retained secundines)	6	2.0	5	2.0
Total	32	11.0	81	32.8

Hysterectomies Not Justifiable

This decision presented no difficulty in the four cases showing no pathology, twelve with no pathology except cervicitis and six where the operation was contraindicated because of the sole finding of pregnancy or retained secundines (Table VII). Obviously this did not tell the whole story, for it seemed improbable that there should not be some cases in the remaining 261, where the hysterectomy was not justified. In order to determine this, these 261 records were critically analyzed to discover if the symptoms and pathology present were of sufficient importance to justify extirpation of the uterus. It was realized that this would not be easy, for the clinical record often does not visualize the picture of the patient as a whole, and other factors, known to the attending physician alone, might influence the decision. It is also difficult in absentia to decide what course one would have followed at the operating table, and so, realizing full well that he was treading upon delicate ground and chagrined to discover that he too was not entirely absolved from criticism, the reviewer based his decision for or against justification for the removal of the uterus on these grounds: (1) age of the patient; (2) minimal symptoms; (3) minimal pathology. On this basis, the following cases were regarded not acceptable for hysterectomy.

CLINICAL DIAGNOSIS CONFIRMED BY PATHOLOGIST

- CASE 1. Age 29. Leucorrhea. Vaginal hysterectomy, primarily for sterilization. Finding, simple hypertrophy of uterus.
- CASE 2. Age 29. Menorrhagia. Total hysterectomy. Finding, hyperplasia of endometrium.

CLINICAL DIAGNOSIS NOT CONFIRMED BY PATHOLOGIST

- CASE 3. Age 30. Abdominal pain. No bleeding. Total hysterectomy. Finding, myoma 0.5 cm.
- CASE 4. Age 50. Menopausal symptoms, no bleeding. Subtotal hysterectomy. Finding, small retention cysts ovaries.

Summary

1. A review of 354 consecutive hysterectomies, performed by seven members of the gynecological, and fourteen of the surgical staff, of the Orange Memorial Hospital, is presented.

2. These 354 hysterectomies consisted of 120 total, 34 per cent, 163 subtotal, 46 per cent, and 71 vaginal types, 35 per cent.

3. The greatest number of cases, 140, or 40 per cent, occurred in the age group 40 to 49 years. There were 167 hysterectomies, 46 per cent, performed in women under 40 years of age.

4. The gynecological service was responsible for 232, 65.5 per cent, of these cases and the surgical service 122, 34.5 per cent.

5. There were two deaths in this series, a mortality incidence of 0.7 per cent in the abdominal hysterectomies and 0.56 per cent in the whole group. Both of these deaths were due to pulmonary emboli in the subtotal operations.

6. Ten patients, 2.8 per cent, had no preoperative symptoms. Abnormal bleeding was the chief complaint of 148 patients, 41.8 per cent, and 308, 87 per cent, complained of bleeding and/or pain and mass in the abdomen.

7. Fibroids were discovered 205 times, 57.9 per cent, in the pelvic examinations prior to operation. Only two cases, 0.6 per cent, were reported as having normal pelves. The preoperative findings appeared grossly to indicate operation in all but five cases, 1.4 per cent.

8. Fibroids were found in 205 of the removed uteri, 57.9 per cent, by the pathologist. The uteri removed abdominally were reported normal (including cervicitis and pregnancy) 22 times, 7.7 per cent. Pregnancy or retained products were reported in 15 cases, 5.3 per cent.

9. Of the fifteen cases showing pregnancy or retained products on pathological examination, eight were recognized preoperatively and seven were unrecognized. Hysterectomy is judged to have been indicated in nine of these patients and not indicated in six.

10. The clinical diagnosis was confirmed by the pathologist in 237 of the 283 abdominal hysterectomies, 83.7 per cent, and not confirmed in 46 cases, 16.3 per cent.

11. In 235 cases confirmed by the pathologist, 83.3 per cent, the hysterectomy is considered justified, and in 16 of the unconfirmed cases, 5.7 per cent.

12. Based on the 283 abdominal hysterectomies, the removal of the uterus is considered justifiable in 251 cases, 89 per cent, and unjustifiable in 32, 11 per cent.

13. In three of the total 354 cases, 0.8 per cent, the type of hysterectomy is judged misused.

Conclusion

From this study it is felt that hysterectomy has been employed too liberally in the past, in the younger group of patients at the Orange Memorial Hospital, and that the incidence of 11 per cent unjustified operations is too high and

Discussion

It is evident, in most hospitals today, that the indications for hysterectomy have been considerably broadened in recent years. Indeed, in many good medical centers, this operation has almost replaced irradiation in the treatment of benign bleeding at or near the menopause. The factors responsible for this radical trend are well known and need not be repeated. Perhaps the pendulum has swung too far and may be expected to return to a more middle course. The decision for hysterectomy is a serious one, for it involves not only the removal of an organ, but constitutes a major break in the pituitary-ovarian-uterine relationship with possible endocrine and neuropsychogenic upheavals. It is incumbent upon the gynecologist to weigh the decision carefully, using all diagnostic means at his disposal and exercising his soundest surgical judgment. Even so, as Wharton² has aptly stated, "in spite of the exercise of our greatest care, in spite of the performance of all pertinent diagnostic procedures, in spite of the fact that we have sought the advice of our colleagues in arriving at the proper conclusions, in spite of all of this, there is not one who has not made unfortunate mistakes." This is not said in defense of indiscriminate hysterectomy, for the removal of a normal uterus without extenuating adnexal pathology or prolapse is to be condemned today as at any time in our gynecologic evolution.

It would seem that the main criticism in this report should be directed toward the number of uteri removed in the younger group, 10 per cent of the total in women under 30, and 46 per cent below the age of 40. This compares closely with the figures found by Miller of 12 per cent and 44 per cent respectively. There is no doubt that this number is too large, and unquestionably some of these cases could have been treated by a more conservative mode of therapy to the advantage of the patient.

What constitutes abuse is difficult to define. To admit this charge, evidence must be produced that there has been undue laxness in indications for operation, that reasonable diagnostic care has not been practiced, and even a hint that remunerative considerations have transcended surgical necessity. With no precedent except Miller's study (32.8 per cent), it is not simple to evaluate an incidence of 11 per cent unjustified hysterectomies. Admitting that this figure is too high and should be reduced, preoperative pelvic findings of 1.4 per cent, in which operation was not indicated or contraindicated, would not appear to suggest a laxness in indications for operation, and confirmation of the clinical diagnosis by the pathologist in 83.7 per cent of the cases would seem to imply that reasonable diagnostic care had been practiced. Therefore, I am disinclined to designate hysterectomy as an abused operation at the Orange Memorial Hospital until more reports of this type are forthcoming from hospitals with well coordinated staffs. Miller is to be commended for his pioneering in this investigation, and it is to be hoped that his effort will stimulate further comparative studies so that the true status of hysterectomy as an operation of necessity can be established.

INVERSION OF THE VAGINA FOLLOWING HYSTERECTOMY*

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INVERSION of the vagina following hysterectomy has long been recognized as a particularly difficult condition to cure satisfactorily. It is often accompanied by troublesome complications such as cystocele, cystitis, incontinence, which demand relief. Many procedures have been devised to meet the indications. Most of these have depended upon some method of suspending the vaginal vault to the fascia of the abdominal wall as described by Brady,¹ or plication to the broad ligaments as used by Payne.² These, of course, depend also upon vaginal plastics. Brady depends on the tension of the anterior vaginal wall to support the bladder and uses only posterior repair of the vaginal tract. These, no doubt, have a field of usefulness. Some can be advantageously repaired by a vaginal plastic alone after the Manchester plan. There is a small group which requires unusual effort.

The purpose of this communication is to describe a procedure which I have developed and used with satisfaction. As far as I know, this plan as used has not been previously described. I offer this as one addition to the armamentarium available for the treatment of this difficult problem.

On July 22, 1944, I was consulted by a patient who presented a condition which would obviously place a considerable strain on any method of repair used. The patient was 66 years of age, had been married forty-six years, and had four children. A complete hysterectomy had been done at the age of 39, or twenty-seven years before. Her general physical condition was good except for diabetes which was then being controlled by diet. The chief complaint was the protrusion of a mass of considerable size which obviously contained bladder and intestines as well as rectum. The bladder symptoms were troublesome. There was not only bladder frequency but partial incontinence. Although the prolapse had existed over several years, there was no ulceration but the mucous membrane was thick and hypertrophied. There was nothing to show where the cervix had been except a scar or dimple. The perineal supports were practically worthless.

While reviewing available literature, my attention was called to the Berkeley-Bonney³ modification of the Le Fort operation which seemed to offer advantages over the usual Le Fort, but this or any other method of suture of the vaginal wall would not be expected to give the needed support to cure such a hernia as this. In fact, I did not find that any method which I had used or with which I was familiar gave promise of satisfactory relief. However, this modification of the Le Fort would answer well as a final step after the anterior and posterior vaginal plastic.

*Read at the Tenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Augusta, Ga., Feb. 12 to 14, 1948.

should be reduced, but from the low rate of preoperative pelvic findings, 1.4 per cent, in which the operation was not grossly indicated and from the confirmatory pathologic support of the clinical diagnosis in 83.7 per cent of the cases, the abuse of the hysterectomy operation in this particular hospital is not conceded.

The author wishes to express his thanks to Dr. Norman F. Miller for his endorsement of this review and generous permission to use his figures for a comparative study and to those members of the staff of the Orange Memorial Hospital who, in such a fine spirit of cooperation, gave their consent for a review of the hospital clinical records of their patients.

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1503 KUHIL AVENUE

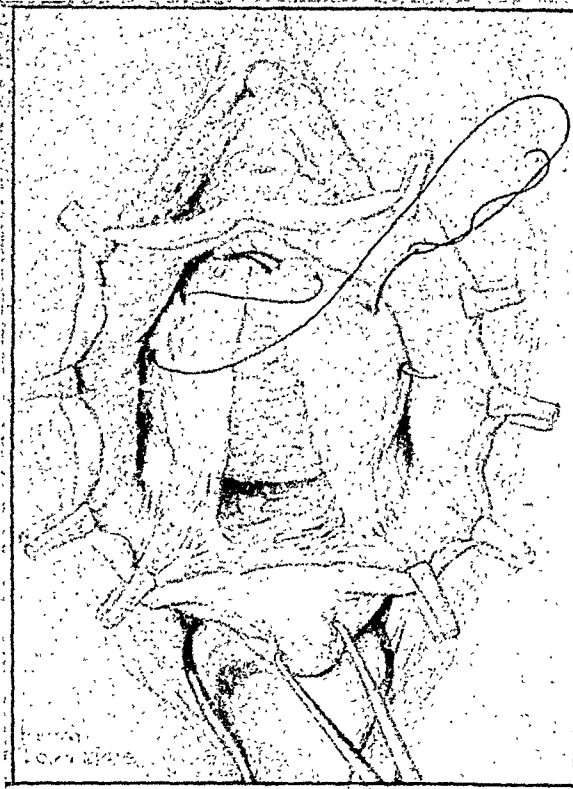


Fig. 2.

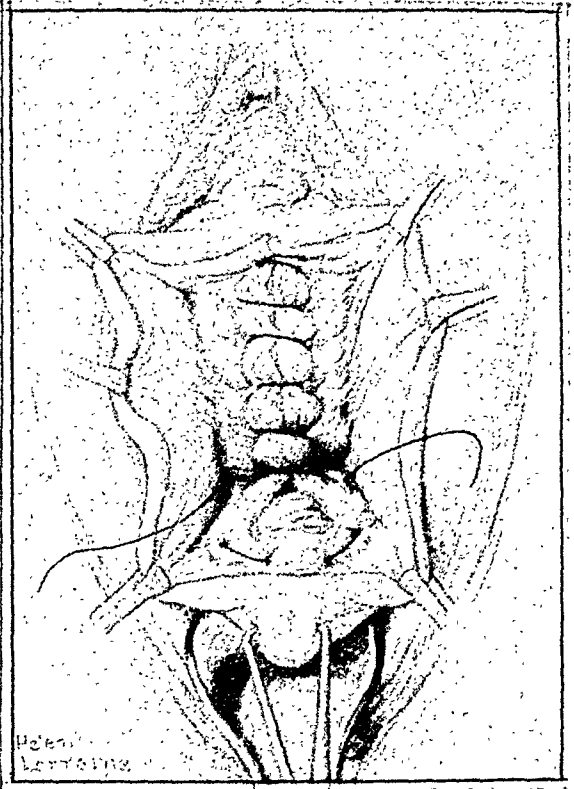


Fig. 3.

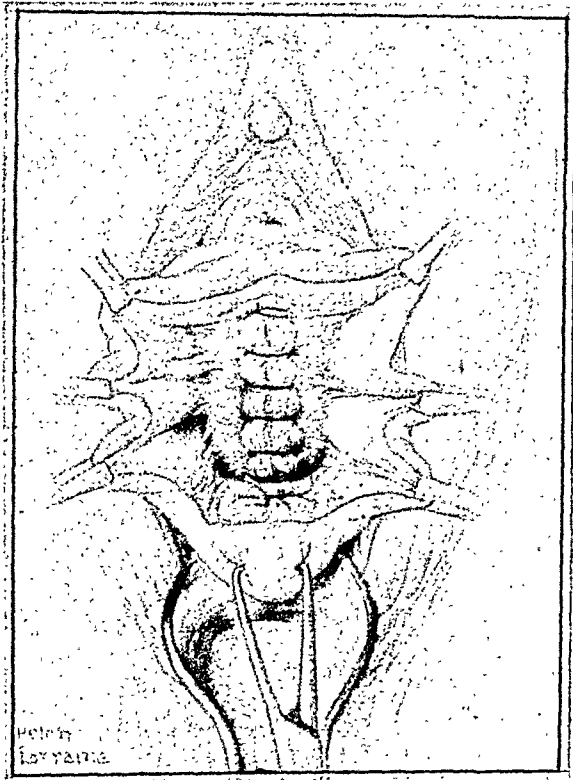


Fig. 4.

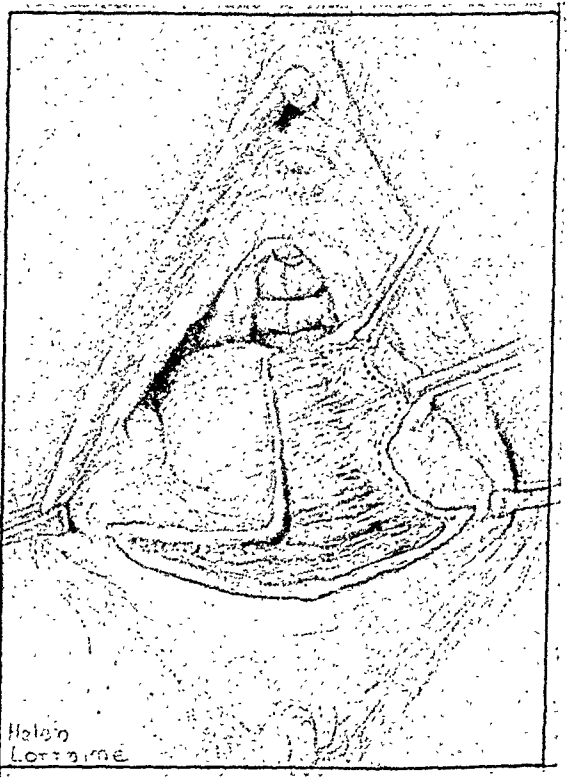


Fig. 5.

Figs. 2, 3, and 4.—Tightening of pubocervical fascia using continuous suture and several mattress sutures for reinforcement.

Fig. 5.—Dissection of posterior vaginal wall. Separation of rectovaginal fascia from vaginal mucosa.

Technique

The technique used consisted first of the usual dissection of the anterior vaginal wall and the pubocervical fascia as shown in Fig. 1. The inverted vault is grasped by a tenaculum at the point where the cervix was removed and the structures placed in slight tension. A short transverse incision is made about an inch from this, then by blunt-scissors dissection the vaginal wall is separated from the pubocervical fascia to a point near the meatus. Prolapse, of course, makes the dissection of the anterior vaginal wall particularly easy. The vaginal wall is separated from the pubocervical fascia first by sharp dissection and then by gauze-covered finger the fascia is exposed as far laterally as needed and carried backward to the scar tissue which originally represented the broad ligaments. Sutures are started near the urethra and carried back to the original site of the cervix. The end of this consists of structures remaining from the broad ligaments. When the fascia was dissected far to the sides, the support was surprisingly strong. Altogether, this gave a shelf of very definite strength which not only held the bladder up but contributed to the pelvic support. Mattress stitches are placed over the urethral sphincter and urethra and give support to these structures. The vaginal flaps are not removed but left for suture as a part of the last step in the operation.

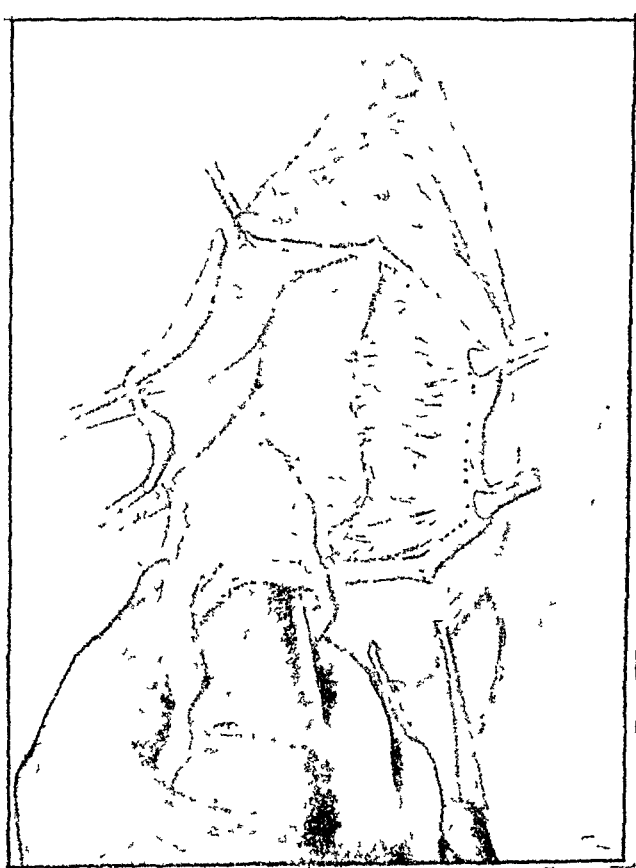


Fig. 1.—Dissection of anterior vaginal wall. Separation of pubocervical fascia. Fascia freed from pubic rami and vaginal mucosa.

The posterior structures are dissected in much the same way as the anterior. A tenaculum is placed on either side of the vaginal tract just below the opening of the Bartholin ducts and placed on slight tension. A strip of tissue connecting these points is removed at the mucocutaneous junction with

scissors. The posterior vaginal mucous membrane is separated by scissors dissection to a point about an inch from the tip of the vaginal vault. The vaginal flaps are dissected to the sides first by sharp dissection and then by gauze-covered finger. These are carried to a point where the rectovaginal fascia is clearly seen and felt. At this point the enterocele was encountered and was dissected, tied off, and excised. This, of course, has nothing to do with this particular method except that it was encountered in this case. The rectovaginal structures are closed by interrupted stitches beginning near the anterior end of the dissection. These stitches are carried to the end of the perineum near the rectum as shown in Figs. 6 and 7. The levators are now sutured (Figs. 9 and 11). At this point the Berkeley-Bonney method of closure of the Le Fort is used, as shown in Figs. 8 and 10. All four flaps, two anterior and two posterior, are brought together by a sufficient number of mattress sutures beginning at the top, each one carrying the previous one higher. Then the suture described as the "crown stitch of Emmet" is carried from the left side of the original incision through such structures available including the levators; when this is tied it raises the perineum high (Fig. 12). This is augmented by any stitches which may be necessary. The skin of the perineum is closed by a fine catgut running stitch which is continuous with the final closure of the mucous membrane. At the completion of the operation, the vaginal tract has the appearance of being entirely normal in support except that the tract is a double-barrel affair communicating at the distal end. This has very much the appearance of a double vagina. When seen recently, this patient stated that she has no symptoms of any sort referable to the pelvis. Although nearly 70 years old, she is carrying on the heavy duties of a boardinghouse keeper. In all respects, the results were perfect.

This procedure is also useful for a large, complete prolapse when there has been no hysterectomy but the uterus and cervix are so atrophied as to be of only slight use.

This is illustrated by a patient who was seen first on June 3, 1945. She was 76 years old, had been married fifty years, and had had six full-term pregnancies, youngest child aged 37 years; all deliveries were said to be normal. This patient was short, rather obese, with pendulous abdomen. Her chief complaints were persistent bladder symptoms and protrusion of a mass from the introitus. This mass also was of considerable size and seemed to consist principally of cystocele but when she stood on her feet the whole vaginal tract inverted. The cervix was represented by a little more than a dimple as these structures were severely atrophied. When first seen, the urine contained considerable pus and the history recorded that the bladder symptoms had been most persistent for a long time. Hypertension was moderate, 176/86. This patient is a portrait painter and likes to be on her feet a considerable part of the day. This fact, no doubt, contributed to the cause of the prolapse and also increased the demand for relief. Every manner of support was tried for her but as the levators were worthless, none of them were of any particular value. The operation was done on Oct. 22, 1946. The technique was essentially the same as in the previous case except that there was a small cervix to which the attenuated cardinal ligaments were attached. The cardinal ligaments were brought anterior to this and sutured, which helped the plan considerably. The posterior vaginal structures were dissected as in the previous case. This hernia also was so large that it was not felt that the fascia would be sufficiently strong to hold it alone. So the vaginal flaps were sutured after the Berkeley-Bonney plan. Anesthesia used in this case was Pentothal sodium. We now use low spinal for vaginal plastics though the anesthesia in this case was entirely satisfactory. The convalescence was disturbed only by a flare-up of cystitis which was noticed after removal of the Foley catheter on the fifth day. Culture was pure colon bacillus and was cleared up very promptly by streptomycin. Her structure supports are perfect.

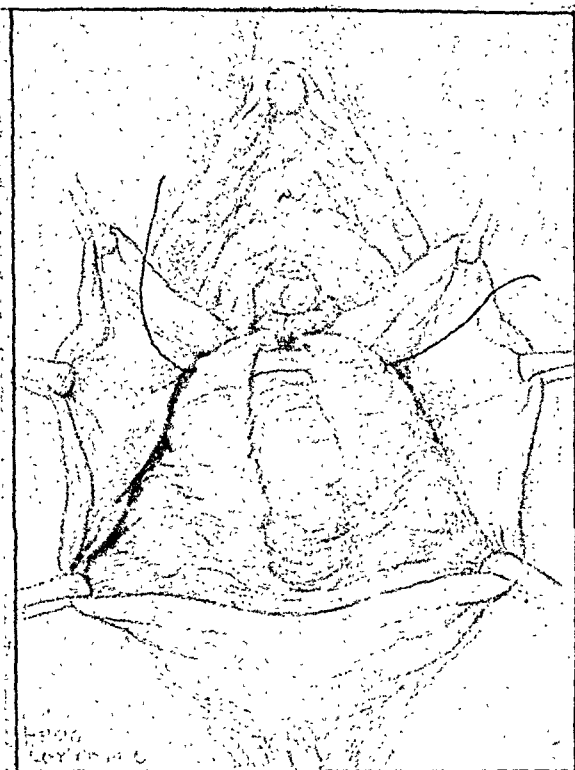


Fig. 6.

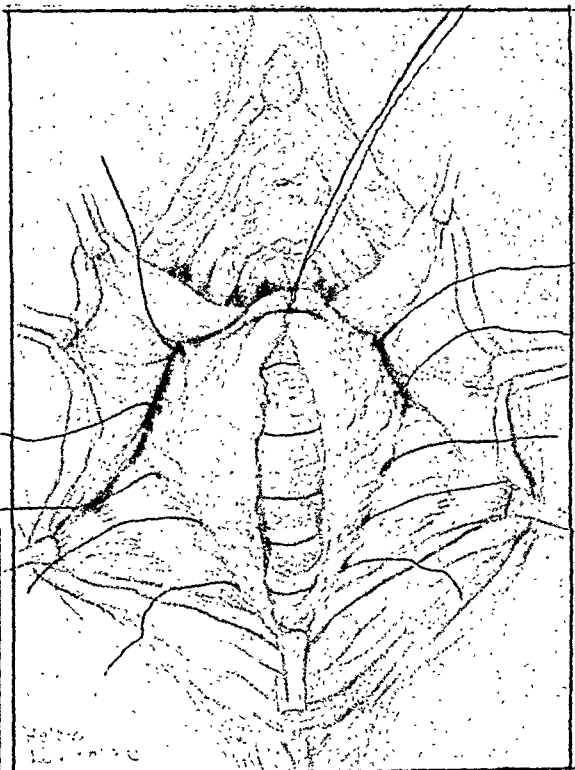


Fig. 7.

Figs. 6 and 7.—Suture of rectovaginal fascia.

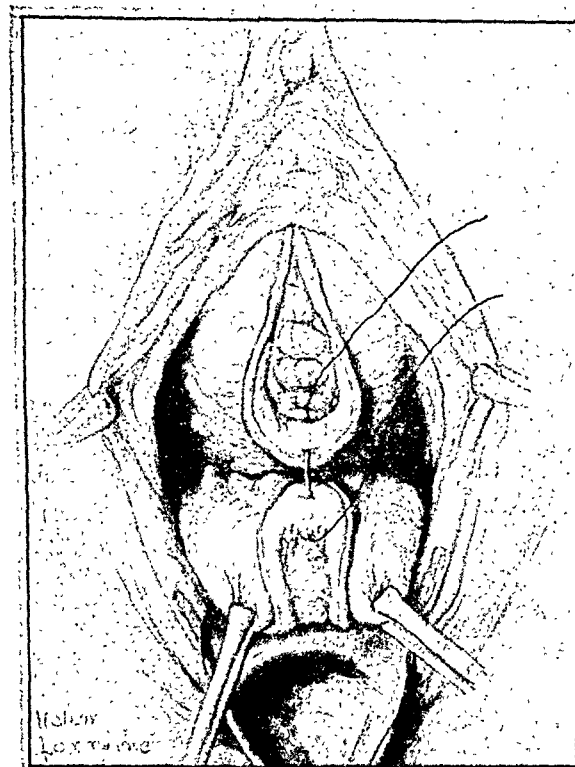


Fig. 8.

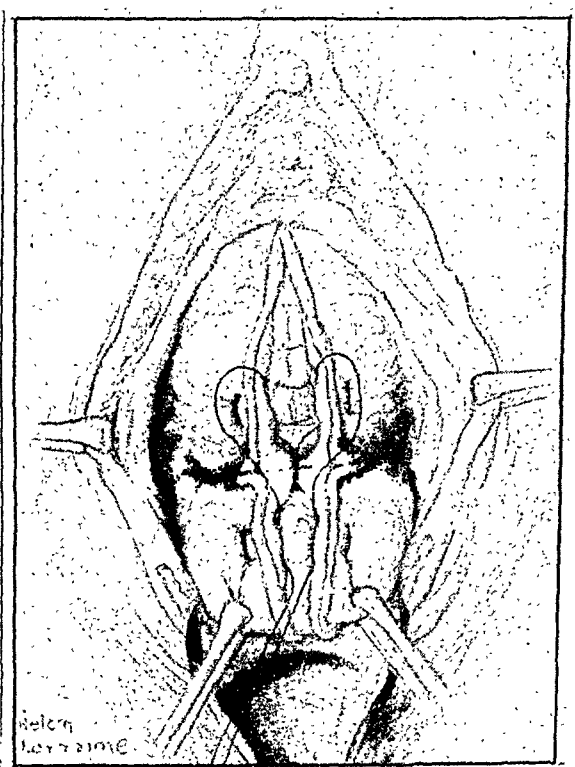


Fig. 9.

Fig. 8.—Initial suture approximating anterior and posterior vaginal walls. No vaginal mucosa is excised.

Fig. 9.—Approximation of incised areas of anterior and posterior vaginal walls by mattress sutures tied inside forming median septum. Each suture carries apex higher.

Discussion

The usefulness of this operation is limited, these limitations being the same as those of any Le Fort operation, in that no provision is made for future marital life, and altogether it is confined to a small group. During the three and one-half years in which these cases were seen, we did 262 vaginal plastics for prolapse, nearly all associated with cystocele and rectocele. This plan has the advantage of being entirely vaginal procedure and is remarkably simple for anyone who is accustomed to doing vaginal plastics. The time required is very short. It eliminates the need for abdominal operation which is undesirable for this particular group, as they do not stand vaginal plastics combined with abdominal operations too well. The second case which I have described would have been entirely unsuitable for any kind of abdominal operation, and very likely no method of suturing the vaginal structures would have been sufficient alone. It seems possible that this procedure might well be used in any case selected for a Le Fort operation as the vaginal plastic is a part of it and offers the advantages of real support. The group suitable for this operation is small but the need for relief is very great.

Summary

1. A method of repair of inversion of the vaginal tract is described.
2. This method consists of a modified anterior and posterior vaginal plastic combined with a modified Le Fort operation.
3. Two cases are reported, which have been most satisfactory.

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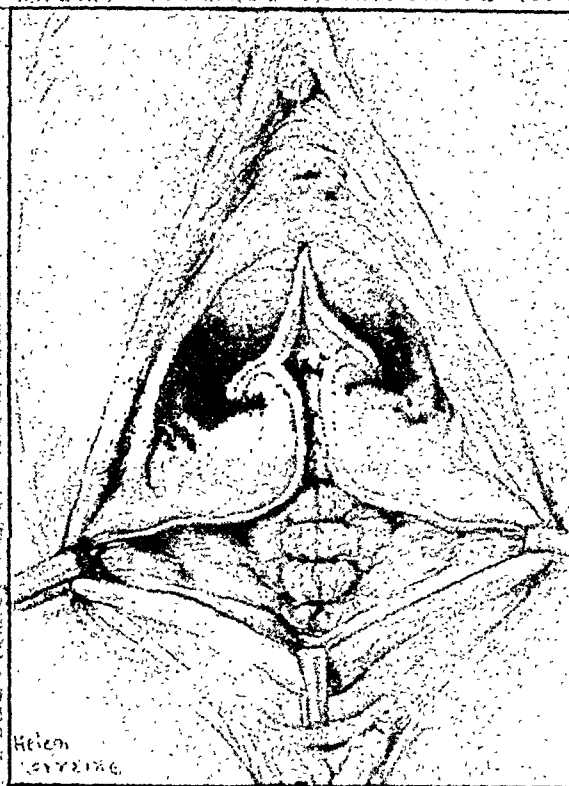


Fig. 10.

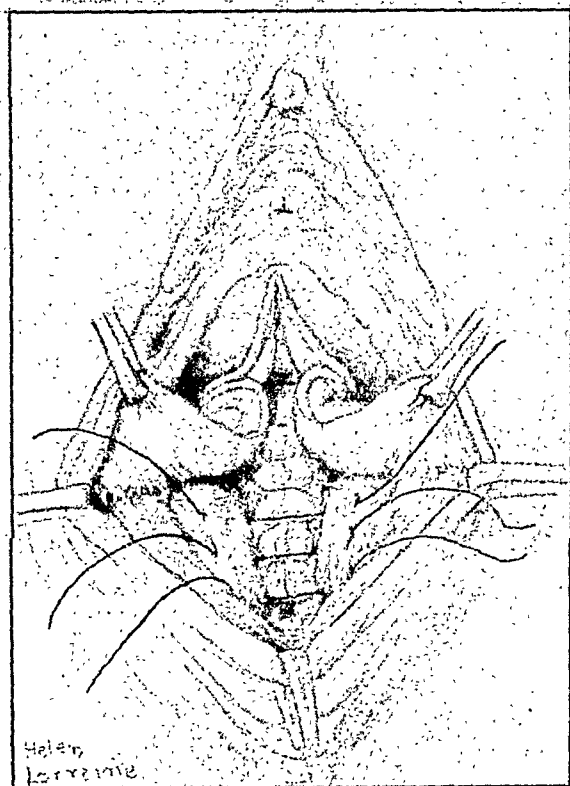


Fig. 11.

Figs. 10 and 11.—Continuation of perineorrhaphy. Sutures of levator ani muscle and fascia.

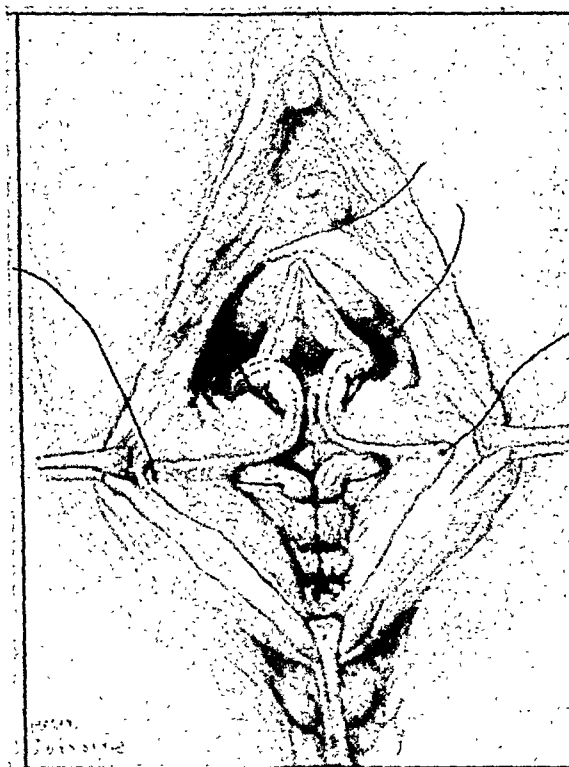


Fig. 12.

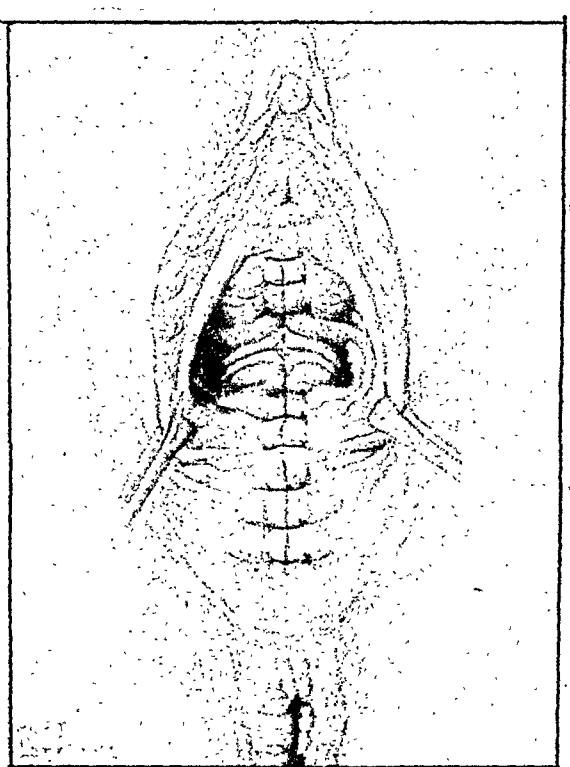


Fig. 13.

Fig. 12.—(a) Perineorrhaphy (continued). "Crown Stitch of Emmet"; additional sutures in perineal fascia as needed. (b) Approximation of vaginal mucosa with interrupted sutures. Fig. 13.—Mucosal closure complete.

per cent of a relatively large series of cases in which there was no head movement interposed between film exposure. In almost 30 per cent of all cases, the movement of the head precluded scientific measurement. This would seem to be an ideal method if the two films could be exposed simultaneously, or almost so.

Ball and Marchbanks,⁸ in 1935, reported a teleroentgenographic process by which the volume of the pelvic cavity calculated from the anteroposterior diameter of the inlet and the interischial spine diameter is compared to the volume of the fetal head calculated from the mean circumference of the fetal cranium. They reported sixty cases in which the circumference of the fetal head was exact to within 1 cm. in 85 per cent and to within 2 cm. in the remainder. The weight of the fetus was predicted to within 8 ounces in 85 per cent and to within one pound in the remaining 15 per cent.

Fray and Pommerenke,⁹ in 1939, presented an ingenious stereoroentgenographic procedure by which a single film is exposed simultaneously by two stationary x-ray tubes, separated from each other by a constant interfocal distance. This eliminated the chief source of error in all double exposure processes, to wit, the movement of the fetus between exposures. They showed that this was very precise in measuring a steel rod, but they had employed it to a limited extent in fetal cephalometry where the variations in rotation of the head presented some difficulties.

In 1940, Thoms and Godfried¹⁰ measured and plotted the suboccipitobregmatic circumference in seventy newborn infants. They showed that this circumference was ovate in shape with the occipital half narrowed and the bregmatic half broadened. In no case illustrated, was there a radius deviation of more than 0.5 cm. and a clinical study shows that by moulding, in any instance, it may become circular.

Guerriero, Arnell and Irwin,¹¹ in 1940, made a study of 503 labors in which the Ball volumetric method of x-ray had been employed. They concluded that "in 38 breech presentations, the correlation between the radiologic findings and the clinical course of labor was not sufficiently close to establish the method as of any great prognostic value." They found it more reliable in cephalic presentations.

In 1941, an excellent critical review of all of the previous work was made by Dippel and Delfs.¹² They stated that most of the popularly employed methods result in an accuracy sufficient for clinical purposes, but that, to be scientifically exact, one must resort to the more complicated ones. They justly criticize isometric grid methods in that correct placement of the grid is necessary and may, in certain cases, be impossible. They favored the Hodge triangulation method as being more accurate. As in all double exposure methods, the fetal head may move between exposures.

Cave,¹³ in 1943, reported a new triangulation method of double exposure on separate films with the position of the patient and cassette identical in each, but with the tube distance varied.

Kendig,¹⁴ in 1946, devised formulas and tables for facilitating pelvic and fetal head mensuration from stereoscopic films.

In labor, the mechanical problem lies not only in a correct knowledge of the pelvic cavity in question, but also of the size and presentation of the fetus. The problem for solution is simply that of propulsion of a bullet-shaped object, the fetal head, through the roughly curved cavity of the maternal pelvis, the latter of which has two dimensions of marked importance: first, the anteroposterior diameter of the inlet, and second, the transverse diameter of the mid-pelvis or the distance between the ischial spines. Some authors have also im-

SIMPLIFIED METHOD OF FETAL ROENTGENCEPHALOMETRY*

Results Checked in 482 Cases

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ACCORDING to Clifford,¹ "Hirsch² has given a concise review of the various attempts to utilize the x-ray for pelvimetry. He points out that five general methods were developed many years ago and all modern methods are, in fact, minor adaptations of these fundamental techniques:

1. *Comparative methods* in which the exposure of the pelvis in the living is compared with a normal specimen taken under identical conditions.

2. *Teleroentgenographic methods* in which the x-ray target is placed far enough from the object to obtain parallel rays and eliminate distortion.

3. *Frame methods*, first suggested by Fabre and Fauchet in 1899, in which a metal frame with its borders notched at centimeter intervals is placed around the patient's pelvis in the plane of the diameter to be measured. The popular Thoms technique is based upon this method except that after the first x-ray the patient is removed from the table and a lead plate perforated at centimeter intervals is placed in the plane to be measured and a second flash exposure made.

4. *Triangulation methods* in which two exposures are made on the same film or on two separate films that are later superimposed. When the x-rays are taken, the shift of the target is a known distance and the target-film distance is also known. "The two shadows of the point in the body are connected and the location of the point above the plate surface may be estimated by a mathematical formula or by a phantom with strings, utilizing the target displacement and the shadow displacement distance as known factors."

This is the principle of the technique first used by Levy and Thumin and by MacKenzie-Davidson in 1898. The methods of Chamberlain and Newell (1912) and Johnson (1927) are recent examples.

5. *Stereoscopic methods* "in which stereoscopic exposures are made and viewed in the regular way. By the use of an illuminated ruler or movable metallic points, placed directly in the phantom image, the pelvis may be accurately measured. . . . It is thus apparent that most of the methods reported in the last few years have been but modifications of the original principles laid down by Varnier, Albert, Fabre, and MacKenzie-Davidson."

Thoms,³ in 1930, presented a study upon 149 infants x-rayed before birth, with the use of a modification of his grid method in which the perforated lead plate was subsequently inserted at the level of the fetal head as determined by palpation. The second exposure then added the centimeter-spaced dots on the film, not on the plane of the pelvic inlet, but in that of the image of the fetal head. Our method is a modification of that of Thoms and somewhat similar to one by Jarcho⁴ which he presented in 1931.

Walton,^{5, 6} in 1931, using his false centimeter chart and two films exposed, one horizontally and one vertically, was able to measure the fetal head accurately when there was no intervening fetal movement.

In a classic paper in 1934, Clifford,⁷ by a stereoroentgenographic method, was able to predict the size of the fetal head in utero to within 0.3 cm. in 97

*Read at the Tenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Augusta, Ga., Feb. 12 to 14, 1948.

triangulation methods. Furthermore, 5 per cent error is no more than that which occurs among a group of physicians who may measure the same newborn head by devices in common usage. A test of its practical value has been that,

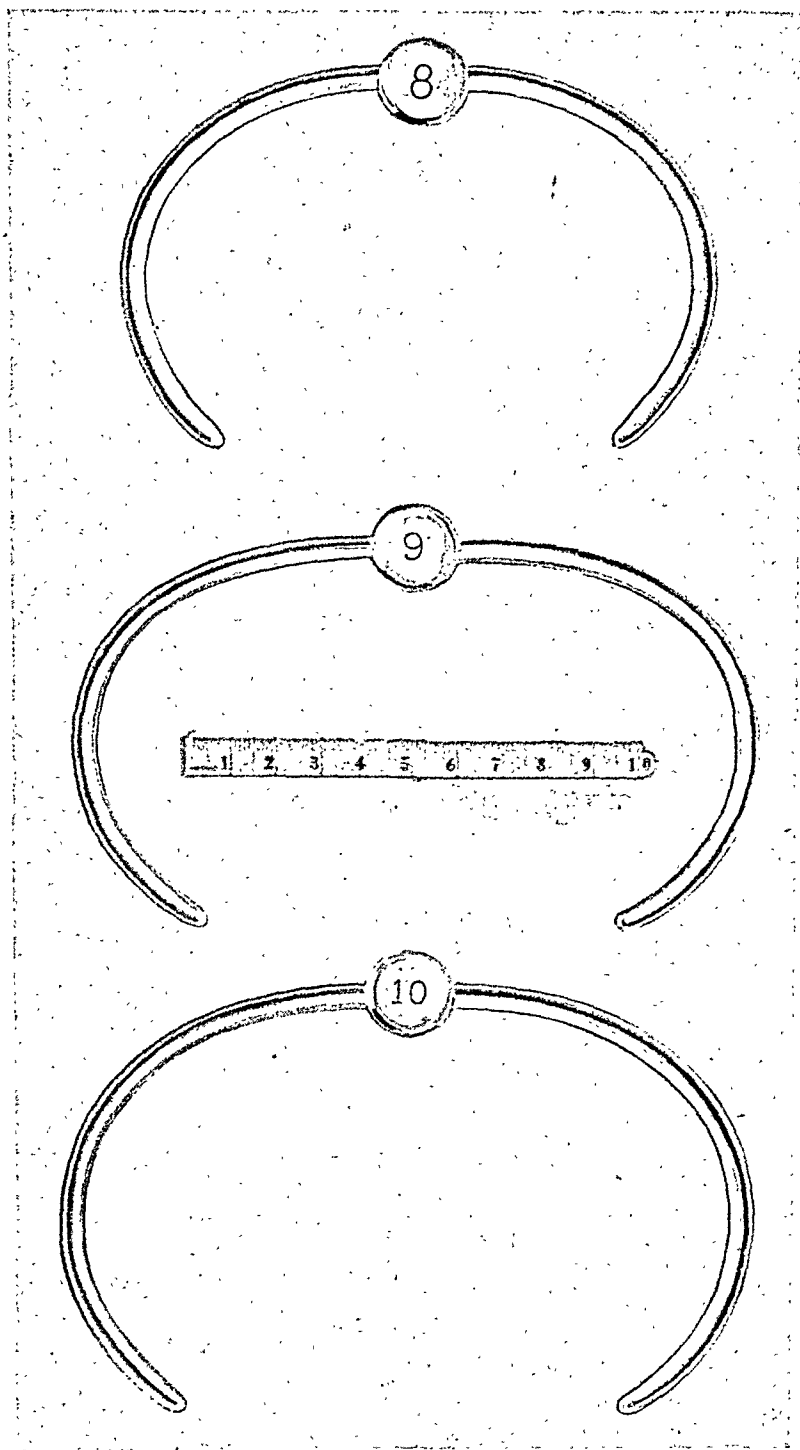


Fig. 1.—Metal gauges to facilitate the measurement of the biparietal and suboccipitobregmatic diameters of the newborn infant's head.

during the seven years of its routine employment in all doubtful labors, the operative delivery incidence has been reduced to approximately one per cent, including forceps and cesarean section. Ninety-nine per cent have delivered

plicated the sacral contour, but in many thousands of deliveries studied, not once has this factor been demonstrated in any case of dystocia as the most important defect.

The concept of the fetal head must be clearly defined. In brief, the head is essentially cylindrical. One end of the cylinder is the face and the opposite end is the occiput with the greatest circumference embracing the biparietal and suboccipitobregmatic diameters. The head is attached to the fetal body by the cervical spine which acts as a fulcrum applied to one side of the cylinder and nearer the occipital end. This arrangement has a tendency to compel the head to traverse the pelvic cavity as occipital presentation. Since in almost all cases the fetal head goes through the pelvic cavity with one end of the cylinder presenting, it is necessary to know only the diameter of the cylinder and this is obtainable by ascertaining either the biparietal or the suboccipitobregmatic diameter, since they are, or can be made by moulding, essentially identical. The knowledge of the length of the head (frontooccipital diameter) is of no practical value in dystocia. Only in brow presentations does the head present with the cylinder sideways, so to speak, and these are very rare, probably not any more often than one in two or three thousand labors. Furthermore, they are indisputably diagnosed by the lateral soft tissue film and when diagnosed, their special management is then in order.

Fetal Head Sizes.—A review of a large number of term newborn heads measured soon after birth demonstrated that they tend to range mainly from 8 to 10½ cm. in diameter, biparietal or suboccipitobregmatic. Under certain circumstances, the biparietal diameter is the greater, under others the suboccipitobregmatic is greater, but these two diameters seldom vary more than one centimeter from each other. The variation is almost always due to head moulding in labor or to lack of it. A narrow midpelvis with a long duration of occiput transverse presentation tends to produce a fetal head with shortened suboccipitobregmatic diameter. A contracted platypelloid inlet with a long first stage of labor will shorten, by moulding, the diameter of the head, which lies between the symphysis pubis and the promontory. This may be either the biparietal or the suboccipitobregmatic, depending upon the presentation at the time. These observations, noted time and again, have been made over a period of a decade in many thousands of labors, exact records of which are available, as well as the measurements of the pelvic cavities from which they came.

Technique of This Study.—The isometric method here used consisted of a single addition to the commonly employed lateral soft tissue technique reported by Snow and Powell,¹⁵ and Dippel and Brown.¹⁶ This addition is that of attaching over the fetal head and as near it as possible a 10 cm. lead scale strapped over the mother's abdomen. It is necessary that this scale lie in a longitudinal plane on an elevation as near the center of the fetal head as possible. When the film is exposed, the scale image then may be used to measure by calipers the diameter of the fetal head in the plane of the biparietal or suboccipitobregmatic diameter, whichever is obtainable at the time. In breech presentation, the scale is placed over the upper portion of the uterus and on a level with the palpable fetal head. The predictable error of the method, if the technique is as exact as possible by a trained technician, is not greater than 5 per cent plus or minus, i.e., 0.5 centimeter. Let it here be stated that the object is for practical aid in prognosticating the course of the labor in question and that it cannot compete with more exacting, but more cumbersome and more costly

vaginally, spontaneously, the only aid having been episiotomy and, rarely, Kristeller expression. The fetal and maternal morbidity and mortality have consequently been at a minimum.

In this series of 482 cases, in 321, or 66.7 per cent, the x-ray measurement was within 0.5 cm. of the actual size of the fetal head. In 427 cases, or 88.7 per cent, the x-ray measurement was within 1 cm. of the true size of the fetal head. In all cases with an error of more than 1 cm., the error occurred in taking the x-ray exposure. The centimeter marker must be placed over the fetal head and in the longitudinal plane, if the correct measurement is to be made; in many of our series, the marker was placed by inexperienced technicians who did not understand the principles involved. Almost without exception, if the marker is placed by experienced personnel, the x-ray measurement will be within 5 mm. of the actual measurement.

Discussion

At the present time, there are several methods of x-ray pelvimetry that quickly reveal the exact size and contour of the pelvic cavity. The ideal is to have such knowledge of the pelvis of every obstetric patient. However, unless one knows the size of the crucial diameters of the fetal head in question, the mechanics of obstetrics is still largely guesswork, as it has been in the past.

Because of the growing popularity of the lateral soft tissue technique in determining the condition of the fetus and the placenta, it would be desirable, in addition, to obtain measurement of the fetal head. This technique makes it possible, but until there is more exact localization of the measuring scale than has been demonstrated here, there can be little reliance upon the prognosis of labor in many of the cases. The study revealed that where due care was taken in placing the marking scale at the level of the fetal head and correct placement of the patient, the error may be kept at 5 per cent. The technique in every case (and this was not always observed in this study) must be supervised preferably by the obstetrician in order to locate exactly the fetal head for application of the isometric scale. Grotesque errors will occur if reliance is placed upon the work of unsupervised technicians.

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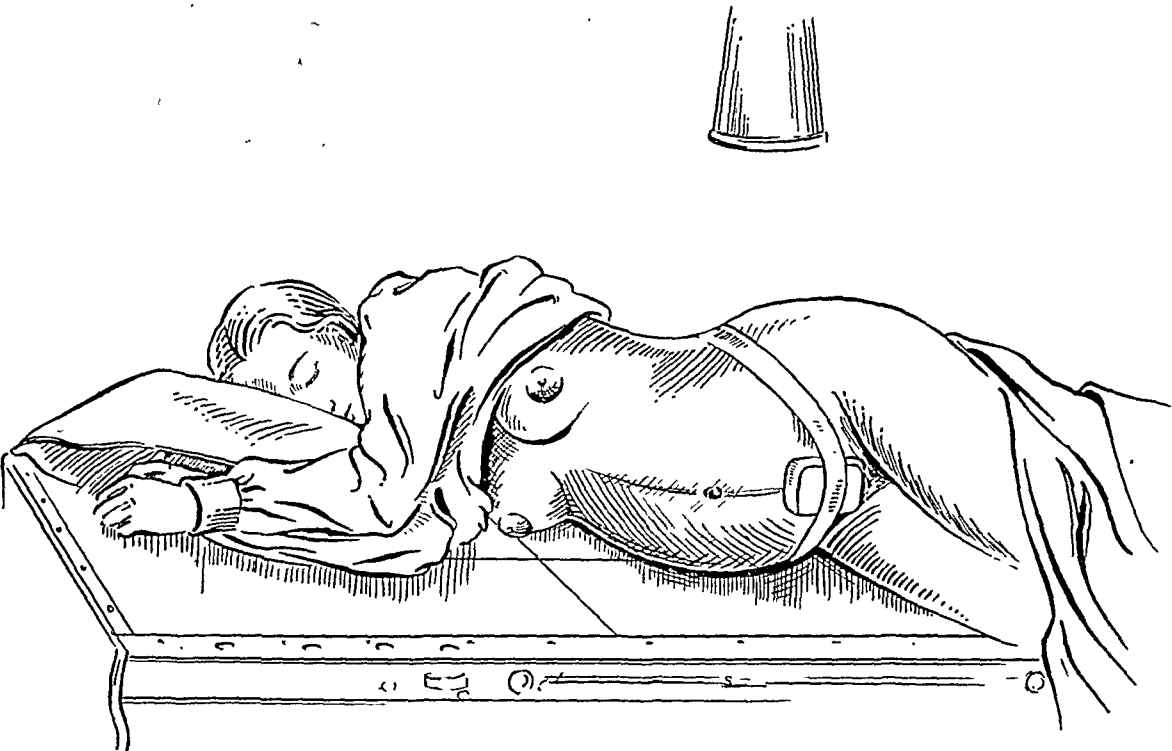


Fig. 2.—Ten centimeter lead gauge strapped over the mother's abdomen and on a level with the greatest diameter of the fetal head at the time of the lateral soft tissue film exposure.

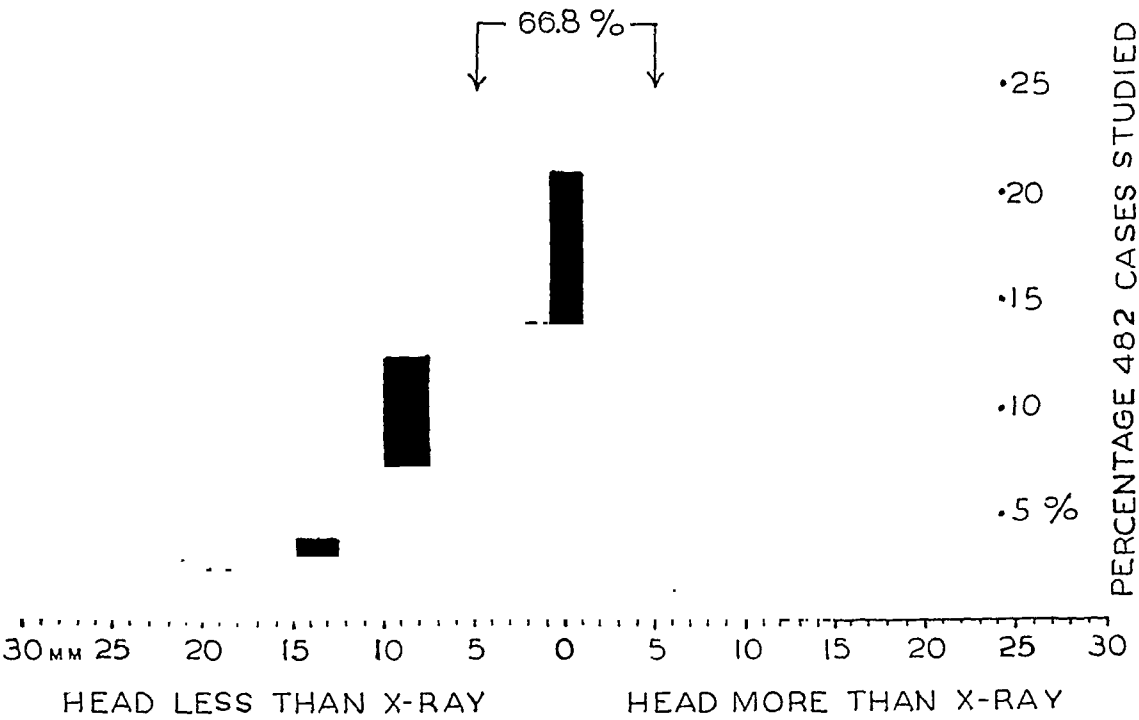


Fig. 3.—Chart showing the degree of accuracy or error in determining by x-ray the biparietal or suboccipitobregmatic diameter of the fetal head in 482 cases investigated.

three months. Careful physical examination of the child was performed at birth and roentgenographic examination of the long bones was made. Roentgenographic studies were repeated whenever indicated by clinical or serologic findings.

The majority of the patients in this study were treated late in the course of pregnancy. Twenty were treated between the sixteenth and thirty-second weeks of pregnancy; fourteen, after the thirty-second week; while only five began their treatment before the sixteenth week.

Since this study began in July, 1946, the period of observation of the patients has been relatively short. One patient developed evidence of relapse three months following treatment. Three patients have been observed for six to eleven months, twenty-seven for twelve to twenty-three months, and the remaining eight patients for twenty-four months or longer. All of the infants have been observed for at least four months after delivery.

Results

Response in the Mother.—Thirty-four of the 39 patients treated for syphilis in pregnancy have obtained a satisfactory clinical and serologic response. The syphilitic lesions disappeared promptly in these patients and no evidence of recurrence has been noted. Thirty-two of them now have a negative serologic test. In the remaining two patients there has been a continuous decrease in titer since the beginning of treatment. With continued observation, the serologic tests of these patients are expected to become negative.

Five patients have developed evidence of treatment failure following penicillin therapy. Three of these five cases showed a rise in the quantitative test for syphilis after delivery. Their children are not infected. The two remaining patients developed serologic evidence of relapse a few weeks prior to delivery, but one of their children appears to have escaped infection. (These patients were not retreated prior to delivery because the rise in quantitative titer did not become significant until parturition.)

Effect of Treatment Upon the Infant.—Thirty-two of the 39 pregnancies have resulted in normal, living, nonsyphilitic infants. Three children were born with syphilis and the infants of four other pregnancies did not live. Of the 32 living and nonsyphilitic children, one child has been observed for four months following delivery, the remaining thirty-one for six months or longer.

The serologic test for syphilis in fifteen of the thirty-two normal children was positive at birth, but became negative in several weeks without treatment. The positive tests were probably caused by a transfer of reagin from the mother, since the maternal serologic tests in these cases were also positive at delivery. Positive serologic reactions in the mother at delivery occurred in 31 of the 39 patients. This was to be expected, since the majority of patients did not receive treatment until late in pregnancy. The titer, however, was decreasing in almost every case.

Occurrence of Syphilis in Infants.—Two of the three children born with syphilis were delivered while their mothers were receiving treatment. In one instance the child was born on the first day of treatment after its mother had received only 240,000 units of penicillin. This patient had entered the hospital in the eighth month of pregnancy because of rupture of the membranes. She was found to have secondary syphilis, and penicillin therapy was started. Labor began four hours later. The child was normal at birth but had a serologic reaction of 20 Kahn units. Three months later the titer had risen to 80 Kahn units, and treatment was begun. The other syphilitic baby was born on the

THE USE OF CRYSTALLINE PENICILLIN G IN THE TREATMENT OF SYPHILIS IN PREGNANCY*†

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PREVIOUS reports on the use of penicillin in the treatment of syphilis in pregnancy indicate that this drug is of considerable value and is more effective than arsenical therapy in the prevention of congenital syphilis.¹⁻⁴ In the early studies, amorphous penicillin was used in doses ranging from 600,000 to 2.4 million units. This report presents the results obtained with larger doses, 4.8 million units, of a purer form of penicillin, crystalline penicillin G.

Case Material and Procedures

The patients in this study consisted of 39 pregnant women with early syphilis. The diagnoses of these patients at the time of treatment were as follows:

Seropositive primary syphilis	2
Secondary syphilis	25
Recurrent syphilis	2
Early latent syphilis	10

None of the patients had had treatment for syphilis except for the two cases with recurrent secondary manifestations. These two had failed to respond to previous penicillin or arsenic-bismuth therapy and developed evidence of relapse during pregnancy. This recurrence of infection was manifested either by a rise in the quantitative serologic test or by a return of the cutaneous lesions. The duration of the infection in the ten patients with early latent syphilis was less than four years and was established by a record of a negative serologic test within that time. Seven of the ten patients were known to have had the infection for less than two years at the time of treatment; two, less than three years; and one less than four years. Thirty-six of the patients were Negro, and three were white.

Each of the patients was treated with a total dose of 4.8 million units of crystalline penicillin G. This was given in doses of 80,000 units every three hours for 60 injections in 7½ days. No additional therapy was administered. After completion of treatment all patients were instructed to return at monthly intervals for quantitative serologic tests and physical examination.

Serologic tests for syphilis were taken on both mother and child at delivery, at monthly intervals thereafter for six months, and then every two or

*Presented at the Tenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Augusta, Ga., Feb. 13, 1948.

†Aided by a grant from the U. S. Public Health Service.

terpreted as healing syphilis. Autopsy revealed bronchopneumonia, pulmonary atelectasis, and pulmonary hemorrhages. Histologic examination of the long bones showed osteitis consistent with healing syphilis.

The fourth death was that of a 1,650 Gm. macerated stillborn infant. The mother in this instance had been treated three weeks before delivery for early latent syphilis of less than two years' duration. Fetal movements had been felt four days before the onset of labor. Roentgenographic examination of the long bones of this child showed severe osteochondritis and osteomyelitis, in addition to numerous pathologic fractures. The severe maceration of the tissues prevented satisfactory histologic examination at autopsy. The death of this infant was probably the result of a syphilitic infection which had failed to respond to the treatment given three weeks previously.

Comment

The results of this study indicate that crystalline penicillin G is of considerable value in the prevention of congenital syphilis, even when given late in pregnancy. All of the patients in this series were in an untreated infectious stage of syphilis, and more than one-third of them began therapy after the thirty-second week of gestation. The effectiveness of penicillin was, therefore, evaluated by the most rigorous circumstances, i.e.: the existence of early untreated syphilis detected late in pregnancy. It has been estimated that approximately 95 per cent of such patients will have congenitally syphilitic children if no treatment is given.⁴ In this study only three living children had syphilis, and two of these were delivered before the therapy was completed.

The two stillbirths in this study were probably the result of severe syphilitic infection. It is likely that the infection in these infants had produced such advanced tissue destruction that no form of therapy would have been successful. For this reason treatment with penicillin should be started early in pregnancy if possible.

The abortion which occurred in the fifth month of pregnancy may have been caused by eclampsia. Another death, that of the child which died three days after delivery, was adequately explained at autopsy by the presence of extensive bronchopneumonia.

It is difficult to compare our results with those obtained with arsenical therapy. In most of the reports on the use of arsenicals in prenatal syphilis, no distinction was made regarding the duration of the infection in the mother or the amount of previous treatment. Despite the lack of accurate comparative data, there is no doubt that penicillin is more effective than arsenical therapy in this condition. It has been estimated that arsenical therapy of patients similar to ours would result in about 15 per cent to 20 per cent of the children having congenital syphilis.^{1, 5}

The reports of other workers using amorphous penicillin showed approximately 6 per cent fetal deaths probably not related to syphilis, and 4 per cent syphilitic infants.⁴ These results were somewhat superior to those observed in the present study. It should be emphasized, however, that a large proportion (35.9 per cent) of our patients were treated in the last eight weeks of pregnancy.

Five (12.8 per cent) of the 39 mothers in this series developed evidence of treatment failure. This relapse rate is comparable to that generally obtained with penicillin in early syphilis after a similar period of follow-up observation. It must be emphasized that a quantitative serologic test for syphilis should be taken at frequent and regular intervals following therapy. This is the only way that relapses in pregnancy can be detected sufficiently early to prevent congenital syphilis. A positive serologic test following therapy or at delivery

fourth day of treatment after the mother had received 2.24 million units of penicillin for secondary syphilis. This child was a premature infant, weighing 2,100 Gm., and had a positive serologic test of 1,280 Kahn units. Roentgenographic examination revealed rarefaction of the long bones proximal to the epiphyses, and the diagnosis of syphilis was made.

The presence of syphilis in these two infants was to be expected, since the course of therapy had not been completed. If the mothers had received the entire amount of penicillin before delivery, the treatment might have been successful. One such instance appeared in this series.

This was a patient with early latent syphilis who delivered a 2,500 Gm. infant on the seventh day of treatment after having received four million units of penicillin. The serologic test for syphilis of the mother was 40 Kahn units while that of the child at birth was 80 Kahn units. Roentgenograms of the infant showed evidence of syphilis of the long bones. This child was not given further therapy and spontaneously developed a negative blood test and healing of the osseous lesions. This, we believe, is evidence that penicillin can effect a cure of the fetus in utero even though it is already infected.

The third child with syphilis was found to have serologic and roentgenographic evidence of the disease at 9 weeks of age. His mother was treated for secondary syphilis at the fourth month of pregnancy, but showed a serologic relapse four days before parturition. She delivered before retreatment could be given.

Delivery During Treatment.—The mothers of three of the children described above delivered during penicillin therapy. Two other patients treated in the last eight weeks of pregnancy also went into labor while receiving penicillin.

In one instance, a mother with secondary syphilis delivered a 2,500 Gm. infant after having received only one million units of penicillin. The serologic test of the infant was doubtful at birth but became, and remained, negative without treatment. There was no roentgenographic or clinical evidence of syphilis in this infant.

The second patient had early latent syphilis of one year's duration and went into labor at the conclusion of penicillin therapy. She delivered a 1,390 Gm. macerated still-born infant three hours later. Fetal heart tones and movements had been noted at the onset of treatment, indicating that the infant died during the course of therapy. Roentgenographic studies of the long bones were not obtained. Although the cause of death could not be determined at autopsy because of the severe maceration of the tissues, the infant probably died as a result of syphilitic infection.

There was only one patient who delivered prior to the thirty-second week of gestation. She had a spontaneous abortion which occurred in the fifth month of pregnancy. The patient had typical eclampsia and was receiving penicillin therapy for secondary syphilis.

Infant Deaths.—Four fetal or infant deaths occurred in this study. Two of the deaths have been described in the foregoing paragraphs.

The third child died three days after delivery. The mother of this child had received penicillin for secondary syphilis six weeks previously and delivered a full-term infant. The child showed evidence of asphyxia at birth and responded poorly to artificial respiration, oxygen, and coramine. He developed a temperature of 105.6° F. four hours after delivery and was treated for aspiration pneumonia. Despite penicillin therapy, death occurred two days later. The serologic test was positive with 10 Kahn units. The mother's serologic test was 20 Kahn units. Roentgenographic examination of the infant's long bones showed slight periosteal thickening, but no definite evidence of osteochondritis or osteomyelitis. Intrauterine disease had apparently been present, as shown by an arrest of bone growth. This had been followed by new bone formation, and the lesions were in-

OPERATIVE OBSTETRICS*

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THINKING in terms of our present obstetrical practice, it is difficult for us to realize that crude and often brutal methods were in use only a century ago. Very little progress had been made since Ambroise Paré rediscovered internal podalic version and Chamberlen the obstetric forceps. For the most part, the care of parturient women was in the hands of more or less ignorant midwives and a physician was rarely called until the woman with severe dystocia was exhausted from the pangs of a blocked labor. Craniotomy was a rather common operation and cesarean section was limited to the unfortunate few whose pelvis were too small to permit a destructive removal of the fetus.

Holmes and Semmelweis had recognized that puerperal fever resulted from contamination, but years passed before the development of the new science of bacteriology made possible a definite proof of its infectiousness. Rokitansky, in 1864, had observed microorganisms in lochial discharges and a year later the streptococcus was identified by Myerh. Two years later Coze and Feltz found microorganisms in the blood of a woman who had puerperal fever. However, it was not until 1879 that Pasteur presented his thesis on "Septicémie Puerperale," reciting his laboratory observations on cultures made from the lochial discharges, the blood, and the peritoneal cavities of women who died from puerperal fever. Since in all of these he obtained pure cultures of streptococcus, he concluded that these organisms were "probably the determinants of that very dangerous disease." Thus Pasteur completed the series of observations begun by White, Gordon, Holmes, and Semmelweis and thereby paved the way for the antiseptic methods introduced by Lister. But many more years passed before modern aseptic methods made possible the obstetric surgery of today.

My own practice of obstetrics began a third of a century ago and it ended with a low-forceps delivery the day before Christmas, 1947. During these years I have witnessed many changes. My preceptor, J. Clarence Webster, in his time was called a radical cesarean sectionist by Dr. DeLee. At the time of his retirement in 1919 he had performed 150 classical and Porro operations with two maternal deaths. During the years after the introduction of the low cervical operation, Dr. DeLee performed several times that number of cesarean sections. Today Dr. Webster probably would be considered ultra-conservative.

The simple and very valuable operation of episiotomy rarely was used prior to 1915, when its value was demonstrated by Brooke Anspach. In my early practice we boasted of our low incidence of forceps deliveries. As late as 1928, I visited one European clinic where, with a yearly average of about

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does not in itself indicate treatment failure, provided the titer is decreasing. Retreatment in pregnancy, preferably with larger amounts of penicillin, is indicated if the patient develops serologic or clinical relapse.

The fact that six of the patients in this series began premature labor during the course of treatment is worthy of comment. Two patients had conditions other than penicillin therapy which could well explain the onset of labor. The membranes had already ruptured in one case, while the other aborted spontaneously after eclampsia. The remaining four cases were treated in the last eight weeks of pregnancy and constituted 28.5 per cent of the fourteen patients receiving therapy in this stage of gestation. This high incidence of premature delivery suggests that the onset of labor may have been related to the large doses of penicillin used in this study. Other workers have also noted the onset of labor during penicillin therapy and have attributed it to therapeutic shock.^{4, 6}

The patient with eclampsia has had a subsequent pregnancy and delivered a normal infant despite the fact that she continued to have a positive serologic test of low titer (4 Kahn units) and received no additional therapy. Five other patients have had subsequent pregnancies and have delivered normal children without further therapy. Similar cases have been recorded in the literature, and it is apparent that treatment with penicillin may protect the mother and baby in subsequent pregnancies.

Summary

Thirty-nine pregnant women with early syphilis were treated with 4.8 million units of crystalline penicillin G and followed for at least four months after delivery. Treatment was started after the thirty-second week of pregnancy in more than one-third of the patients.

Six patients went into premature labor during penicillin therapy and two of their children were born with congenital syphilis. One patient developed a serologic relapse prior to parturition and delivered a syphilitic child. There were four infant deaths, two of which were probably caused by syphilis. The remaining 32 children are now living and nonsyphilitic.

Five (12.8 per cent) of the 39 mothers have shown evidence of relapse of their syphilitic infection.

The results obtained in this series of patients with early infectious syphilis treated in the late stage of pregnancy indicate that crystalline penicillin G is an effective therapeutic agent in prenatal syphilis.

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Western Journal of Surgery, Gynecology and Obstetrics. These papers indicate gradually changing views regarding the management of pregnancy and labor. Data covering my 11 years in Wilmington have now been added making it possible to cover a twenty-eight-year period.

Spontaneous delivery, frequently after a mediolateral episiotomy, occurred in 1,100 cases; there were 595 low forceps, 461 midforceps and 28 high applications. Cesarean sections were performed 125 times, with 64 classical, 48 low cervical and 13 Porro operations. Six patients had vaginal hysterotomies and forceps deliveries. Version and extraction were employed 14 times and there were 99 breech presentations. The Piper forceps was applied to the aftercoming head in 30 deliveries. Out of a total of 2,456 babies, there were 26 sets of twins and one of triplets. Thirty-one babies were still-born and 36 others died during the first month of life, a fetal loss of 2.71 per cent. Five women died, just over 2 per 1,000 women.

Prematurity, under seven months, was the major cause of death for 20 of the babies who died the first month. Three babies died during an outbreak of "diarrhea of the newborn." Four had very serious heart defects proved by autopsy. Hemorrhagic disease of the newborn killed two. Three had marked atelectasis proved by x-ray or autopsy. Erysipelas of the penis following circumcision killed one. Erythroblastosis was responsible for one. One developed pyelitis and died on the eighteenth day. Another was lost through virus pneumonia which developed after going home.

Fifteen of the stillborn babies were macerated, having died before the onset of labor. Erythroblastosis caused a few of these deaths. True knots of the cord and extreme twisting caused others. None resulted from syphilis; in fact, only two of my patients ever indicated any evidence of this condition. Of the sixteen babies lost during labor, 5 were monsters (anencephalic); three died as a result of premature separation of the placenta; one, a five and one-half month fetus, died during labor while the mother was unconscious with a severe nephritic toxemia; seven normal babies were lost as a result of prolonged tests of labor prior to operative interference, or as a result of pressure on the cord during an easy normal labor. The loss of these seven babies led to more frequent checking of the fetal heart rate and earlier operative interference when changes in the rate suggested impending asphyxia. In one case, partial premature separation of the placenta made it necessary to accomplish a rapid delivery by classical cesarean section. Thirty minutes of artificial respiration were required for resuscitation. In this case the baby developed a beautiful body but was a total idiot. We now have definite experimental proof as well as clinical that fetal asphyxia rapidly destroys brain cells and every effort must be made to avoid it during labor.

Five mothers were lost. One died in convulsions some twelve hours after her delivery; one had an influenzal pneumonia and one developed a paralytic ileus with an unrecognized appendicitis following delivery by cesarean section a month or more after term. Autopsies were obtained on these three. More recently two more mothers died, one from a pulmonary embolus within an hour after delivery; the other with a thyroid crisis and heart failure. Autopsies were refused in these cases.

Approximately 5 per cent (125) of my patients were delivered by cesarean section. The one woman who died from ileus and appendicitis had been delivered through the natural passages four times previously but this time the baby which weighed just under 11 pounds was too large. Several of the other women who required cesarean section had been delivered by me one or more times before they developed a baby that was too large for their

1,800 deliveries, they reported only 10 or 11 forceps deliveries and some 50 cesarean sections each year. When, in 1920, Dr. DeLee presented his paper on "The Prophylactic Forceps Operation," he was generally condemned by the members of the American Gynecological Society. Today we realize that a low-forceps delivery may be much safer for both mother and infant than a more prolonged labor with an excessive use of Kristeller pressure in the effort to record another so-called normal delivery.

About 1861, Simpson stated that induction of premature labor a century earlier was "perhaps the greatest improvement that has ever been made in the practice of midwifery." However, the greatly reduced risk of the cesarean operation has materially lessened the incidence of premature induction of labor several weeks before term. Induction of labor at term, on the other hand, is now being advised by a few obstetricians and they have demonstrated that, properly employed, it is a safe and possibly a conservative procedure. Induction at term must not be confused with induction of premature labor. If the cervix is patulous and the head fixed in the pelvis, labor may be expected to follow shortly after the membranes are ruptured, and available data indicate that the duration of labor on the average is shortened. If the head is not engaged or the cervix is rigid with no effacement, artificial induction of labor rarely is justified.

Craniotomy a century ago was a rather common operation. Most of us will agree that it is no longer proper to consider it unless the fetus is very abnormal or already dead. The extraperitoneal cesarean section, as developed by Waters, or the more recent modification of Norton, is probably less dangerous for the mother than a craniotomy.

About 1920, Potter of Buffalo reported before the Philadelphia Obstetrical Society 1,113 labors with 920 versions and 80 cesarean sections. However, his immediate fetal mortality was 6.7 per cent and those who tried his version soon realized that it was not a proper substitute for normal labor. Nevertheless, he has added to the technique of a valuable operation which has definite indications and is at times the only proper procedure.

Twilight Sleep appeared just as I was starting my private practice of obstetrics. The group with which I worked in Chicago was much interested in the development of nitrous-oxide-oxygen analgesia and eventually I adopted the best parts of both methods, using heroin with the hyoscine, rather than morphine, and limiting the gas to the second stage of labor. More recently I have used Demerol with hyoscine since heroin is no longer available. In 1920, while discussing a paper on the use of ether in obstetrics I made the following statement: "Recently I have been using nitrous-oxide-oxygen analgesia intermittently for both mid- and low-forceps deliveries as well as in normal labor. The nitrous oxide-oxygen is given to a deep analgesia or light anesthesia while the forceps is applied. The mask is then removed, and thereafter the gas is given intermittently as in normal labor. The patient is instructed to bear down during contractions while gentle traction is made on the forceps. For primiparas, I do a primary posterior episiotomy. There is usually an easy delivery with a minimum of traction pressure on the head." After using this plan for some thirty years, I still believe it is safer for the fetus than use of the greater traction that is required when the woman is deeply anesthetized and unable to assist.

Many years ago, I began making yearly checks on my obstetrical work so that I could compare my results with those reported by others. In 1926, a survey of my first 500 deliveries in Milwaukee was presented before the Chicago Gynecological Society. Later, in 1941, a complete report on the obstetrical part of my private practice in Milwaukee was published in the

Great progress has been made within recent years and both infant and maternal mortalities have dropped materially since 1940. It is my belief that the next great change in obstetric practice will be in the development of groups who will work as units. Those who have tried this plan have found that it makes possible an improved service to the patients and greatly lessens the physical strain on the men in the group. Obstetricians working in such groups will be able to give better service to the women in labor as well as in the office during prenatal care, since a continuity of service is possible. One man would be on duty at the hospital all of the time and patients in labor would be watched more carefully than at present. Too much is now being left to the inexperienced judgment of nurses and interns. After being up all or most of a night, a doctor would be assured adequate rest the next night. Patients would no longer need to change office appointments because the doctor was called to the hospital. One of the group would be on duty in the office during the entire day.

The young obstetricians who are being certified by the American Board today have had opportunities denied to those of us who began specialty training thirty and forty years ago. We rightfully expect from them continued progress toward making pregnancy and labor still more safe for both mother and baby.

natural passages. Three cesarean sections performed in 1945 and 1946 were on women whose pelves were ample for babies of average size; one had been delivered twice by forceps and one had a record of four normal labors; one was a primipara with an oversized baby.

A cesarean section still is far more dangerous than delivery through the natural passages. Moreover, the mortality associated with a single cesarean does not tell the entire story, for risks multiply with each succeeding pregnancy. I sometimes wonder if we are entirely justified in discontinuing premature induction of labor when there is evidence that the baby will be too large if the pregnancy continues. I feel certain that in the future fewer women will be permitted to continue very long beyond term.

Breech deliveries are somewhat more dangerous for the fetus. One of the babies that I delivered easily, without the use of forceps on the aftercoming head, is somewhat spastic, suggesting a possible birth injury, but a congenital defect is equally probable. One of the most serious objections to version and extraction is the increased danger to the baby from the breech birth. I have rarely attempted external version on any of my private patients since such a high percentage will convert spontaneously during the last month of pregnancy. Furthermore, I always recall that one of my former patients lost a baby as a result of a forcible conversion under anesthesia, while under the care of one of my friends who routinely tries to convert all breech cases to vertex.

High forceps is no longer favored except in an occasional multiparous woman where there is no evidence of disproportion. I have reported a rather high percentage of midforceps deliveries since I have so classified practically all cases requiring rotation from the transverse or posterior position even though the caput may at times make the head appear to have reached the perineum. All statistics indicate that an outlet forceps delivery fairly early in the second stage is safest for the infant since it shortens the labor, thereby lessening the damage from edema of the brain and the risks of asphyxia from pressure on the cord.

There is no reliable data on fetal mortality 100 years ago, but we know that it was very high during the first year of life. Although it is evident that the members of this group will have a gross loss of around 3 per cent, counting stillbirths and deaths during the first month of life, most hospitals are reporting a loss of about 5 or 6 per cent of the babies born in the institution. It seems obvious that statistical information should be required on all hospital deliveries and those physicians whose records show abnormally high infant or maternal mortality should be definitely restricted. Every man's work should be checked separately and judged on his results.

One hundred years have now passed since James Y. Simpson began the administration of ether and chloroform during the painful stage of labor. Obstetric progress has been slow, so slow that at times no progress could be noted for long periods. It was over 100 years after Dr. Physick and Professor Horner had demonstrated in the dissecting room the possibility of an extraperitoneal cesarean section that Waters developed his operation. The year I graduated from Rush Medical College (1909), Dr. A. L. Smith of Montreal read a paper before the American Gynecological Society, entitled, "We Are No Longer Justified in Sterilizing Every Woman Who Has a Cesarean Section." Today we can state that the extraperitoneal cesarean operation has removed the earlier reasons for craniotomy or a Porro section in the contaminated case. However, contamination never was a proper indication for the Porro cesarean hysterectomy since it could not be performed without infecting the peritoneal cavity.

nonpregnant women to compare with the mean plasma volume of a group of pregnant women. This author points out that the range of plasma volume in pregnancy is greater than in a group of nonpregnant women. Hence, it would appear that the changes in the plasma volume of an individual patient during pregnancy should only be compared with her own nonpregnant level. This volume level, ideally, should be determined in the prepregnant state. However, for obvious reasons this is not feasible. Therefore, a later postpartum determination must suffice for the nonpregnant level. In addition, a prelabor decrease in plasma volume was not noted. This is understandable because, with only one antepartum observation, one would be unable to detect the peak of plasma volume increase.

It is obvious that there is no agreement regarding the degree of increase in plasma volume and the time in gestation when the maximum change is present. The occurrence of a significant prelabor decrease is also in question.

With the exception of Chesley's work,^{5,6} extracellular fluid has not been studied during normal pregnancy. Using sodium thiocyanate, he was able to measure the extracellular fluid volume on a large number of pregnant women. Although Chesley's observations were scattered over many patients, a definite trend was noted. He showed that as pregnancy progressed there was an increase in the "available water." Loss of available water in the puerperium was also measured, but because of the interval of time between measurements, he felt that his observations were not particularly valid. In addition, Chesley interpreted certain data obtained on normal pregnant women as suggestive of an intracellular transfer of water to the extracellular spaces.⁶

Material and Methods

Ten subjects were used in this study and 6 to 12 observations were made on each. It was our desire to study many patients, but a composite study such as this on a larger group of patients would not be practical since the radioactivity determinations alone are time-consuming and expensive. The patients who were used as subjects were healthy multigravida and primigravida women. Their diets were adequate and unrestricted and no medication of any kind was taken during pregnancy or the puerperium. Observations were made at 5- to 6-week intervals throughout pregnancy; the earliest determination on one patient was made 230 days prior to delivery. An attempt was made to have the final prepartum observation as close to the onset of labor as possible and a determination was made during early active unmedicated labor in one case. In the puerperium, volumes were determined at the end of the first week in 5 cases. The last postpartum observations were made on the 26th to the 66th days of the puerperium.

Plasma volume was measured by using the blue dye T-1824. The technique used was that described by Gibson and Evans.³ In order to answer a previous suggestion that the dye might not be completely mixed and possibly trapped at the placental site,⁴ the following procedure was done. A patient with a normal term pregnancy while under spinal anesthesia and prepared for an elective cesarean section, was given 10 mg. of T-1824 and 50 c.c. of whole fresh radioactive red blood cells in the left antecubital vein. Prior to this injection, the left uterine vein had been cannulated with polyethylene tubing. The tip of this tubing was placed as far into the uterus as possible. Simultaneous samples of heparinized whole blood were then withdrawn from the cannulated uterine vein and from the right antecubital vein at 1, 3, 5, and 7 minutes after the injection of the blood and dye. When the

Original Communications

PLASMA VOLUME AND EXTRAVASCULAR FLUID VOLUME DURING PREGNANCY AND THE PUERPERIUM*†

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Introduction

THE purpose of this study was to investigate the changes that occur during normal pregnancy in the circulating red-cell mass and plasma and extravascular fluid volumes. It was felt that determining the normal relationship between these three compartments in uncomplicated pregnancy might aid in evaluating changes occurring in abnormal pregnancy.

This report presents results of the simultaneous determinations of plasma volume and extravascular fluid volume. A subsequent paper will give the results of the measurements of the circulating red-cell mass as determined with the radioactive isotope of iron, Fe 55. Another paper will discuss the changes in the capillary bed in pregnancy.

Previous studies of plasma and extracellular fluid volume have been confined to observations of one or the other. To appraise adequately the changes in the vascular and extravascular compartments, simultaneous and frequent determinations on the same patients must be made. In the work published thus far, this has not been done. Dieckman and Wegner¹ in 1934 reported the results of plasma-volume changes in pregnancy as measured with the dye, Congo red. Their finding of a 25 per cent average increase in plasma volume in pregnancy is lower than the values found in subsequent studies.

Thomson et al.² in 1938 reported the results of plasma volume determination using the Evans blue dye technique.³ These investigators found that plasma volume increased progressively and reached a maximum in the ninth lunar month. This value was 65 per cent higher than the "average normal nonpregnant" value. A prelabor plasma-volume decrease was noted and they state that normal nonpregnant levels were reached by the end of the second week in the puerperium.

McLennan⁴ has recently published the results of plasma-volume determinations in pregnant patients at term and on the seventh postpartum day. In analyzing his material, this author uses a mean plasma volume determined in

*Résumé of the material contained in the first two of this series was presented, by invitation, before The American Gynecological Society, Williamsburg, Va., May, 1948.

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TABLE I. PLASMA AND EXTRAVASCULAR FLUID VOLUME IN PREGNANCY AND THE PUERPERIUM

CASE NO.	PARITY	WEIGHT IN POUNDS	DAY ANTE PARTUM	DAY POST PARTUM	PLASMA C.C.	VOLUME C.C./KG.	LVHCT*	EXTRA-VASCULAR C.C.	FLUID VOLUME C.C./KG.
5	2	134.5	159		2810	46.0	41.4	11,850	194
		140	93		3600	56.5	36.3	14,350	223
		145.5	53		4400	66.5	33.8	15,150	230
		151.5	11		4400	64.0	33.8	15,400	224
				7	3000		30.9	10,400	
6	1	127		66	2730	47.0	36.1	12,600	219
		109.5	172		2800	56.5	39.9	10,050	212
		119	131		3366	62.0	37.7	11,900	220
		128	90		4100	70.5	34.7	12,700	218
		135	49		4160	68.0	32.5	16,300	266
		145.5	3		3460	52.4	35.2	23,200	318
		119		45	2710	50.1	38.2	10,600	196
7	1	100.5	208		2154	47.7	39.2	13,300	293
		105.5	161		2566	54.0	35.3	11,234	304
		109.5	123		3080	61.6	32.2	11,000	220
		119.5	82		3480	64.0	31.1	13,000	239
		114	41		3750	72.0	28.1	14,800	284
		119.5	0		3300	60.7	32.2	15,500	286
		104.5		26	2180	46.2	37.4	9,750	206
8	2	111	132		2800	56.0	37.6	8,230	164
		120	91		3110	57.0	35.6	10,700	231
		124	50		3315	58.8	32.5	11,100	196
		130	8		3060	51.7	35.7	14,000	237
		118.5		7	2640	49.0	35.5	12,100	224
		109.5		33	2360	47.5	38.0	8,650	174
11	1	151.5	148		3973	57.3	35.9	16,100	239
		155	111		4630	65.5	32.3	20,600	280
		157	78		5285	74.0	31.7	14,900	204
		160	39		5425	75.5	29.4	15,600	214
		160	4		4975	68.5	32.5	16,700	228
				7	3500		37.8	16,600	
				65	3410	50.0	34.6	15,000	220
12	1	120	215		2440	44.8	37.0	11,000	202
		124.5	180		2714	48.0	35.4	11,750	207
		133.5	138		3110	51.3	34.2	11,600	193
		134.5	90		3515	57.5	31.9	11,000	181
		138.5	53		3410	54.1	33.6	14,500	230
		149.5	8		3710	54.5	32.9	16,800	247
		149	5		3710	54.7	32.9	17,150	253
13	1	120		30	2680	49.2	33.7	11,200	203
		148	200		2930	32.7	39.6	14,200	212
		162	140		3290	44.5	37.5	15,000	204
		169.5	104		3510	45.5	34.4	15,400	200
		165.5	68		4400	58.7	32.5	14,500	194
		178	24		4200	51.7	35.2	25,500	310
		181.5	1		3710	45.0	36.5	20,000	242
15	1	153		30	3080	43.7	38.7	13,900	197
		122	233		2850	51.0	39.6	11,700	210
		126	189		3380	59.0	36.5	11,800	204
		133	147		3720	61.5	34.6	12,700	210
		140	97		3600	57.0	35.0	14,300	224
		145	55		3960	60.0	33.7	12,350	187
		150	18		4000	62.3	33.3	15,400	225
		150	11		3840	60.8	32.0		
				labor	3260		34.1		
				1	2950		36.5		
				3	3340		35.4		
		130		6	3520	59.6	34.4	12,600	213
		122		30	2710	49.0	37.6	12,150	218

plasma samples were checked photolorimetrically, the dye concentration in the uterine and arm samples was the same. No difference was found in the radioactivity of the blood samples which were withdrawn simultaneously. It is felt that this is evidence that blood is not trapped at the placental site during its circulation through the uterus in a full term normal pregnancy.

Extracellular fluid was measured by the use of intravenous 5 per cent sodium thiocyanate. Thiocyanate was determined using the method described by Chesley.⁷ Serum and urine samples were checked in triplicate. Since the plasma volume is included in the thiocyanate space, extravascular fluid volume could be calculated.

Procedure

On the morning preceding the test the patients were admitted to the hospital. Following a fat-free lunch, an injection of 5 per cent sodium thiocyanate was given intravenously. Eighteen to twenty hours were allowed for equilibration of the thiocyanate. All of the urine voided during this period was collected. Fluids were not restricted and patients were active about the ward. The next morning, under fasting, basal conditions, 10 mg. of T-1824 and 100 c.c. of whole fresh radioactive blood were given to measure simultaneously plasma volume and the circulating red-cell mass. A serum sample for thiocyanate concentration was taken prior to this injection. Heparinized samples of whole blood were then withdrawn without stasis at ten-minute intervals for fifty minutes. The procedure was then completed exactly as described in previous papers.^{3, 5}

Results

Plasma Volume.—The absolute plasma volume values obtained in 10 patients during the course of pregnancy are individually illustrated in Fig. 1. The nonpregnant plasma volume levels were taken as those observed approximately thirty days postpartum. At this time these latter volumes were found to be about 5 per cent of body weight, this percentage being generally accepted as the normal adult value.

Without exception, it will be noted that there was a progressive increase in plasma volume up to approximately 68 to 5 days prior to the onset of labor. This increase in volume ranged from 955 c.c. to 2,015 c.c., with an average increase of 1,366 c.c. In 8 full term pregnancies, there was an average prelabor decrease of the plasma volume of 347 c.c. from its mean maximum value. The plasma volume did not decrease but the prelabor values remained stationary in the other cases. One was a full-term mild pre-eclamptic pregnancy (Case 12) and the other a case of premature labor (Case 5). The plasma volumes observed on the seventh postpartum day were greater than those determined one month after delivery (Table I).

During the course of this study, the determinations on two patients were such as to deserve special mention. In Fig. 1 (Case 5) are shown the changes in plasma volume observed in a patient who delivered prematurely. On the 128th day prior to the estimated date of confinement, the maximum plasma volume was attained. This volume was again observed 80 days prior to the estimated date of confinement which actually preceded the onset of premature labor by 11 days. At this time the patient was delivered of a living infant weighing 2,438 Gm. One wonders whether this lack of change in plasma volume reflects the impending onset of premature labor. Because of the lack of data in previous studies of the plasma volume changes in the early puerperium, several determinations were made during this period on Case 15.

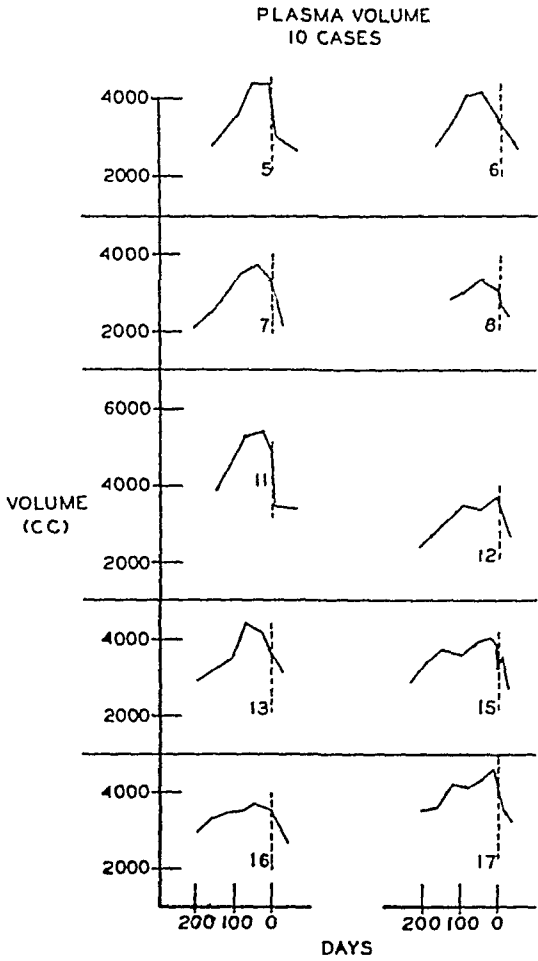


Fig. 1.

PLASMA VOLUME CHANGES
ASSOCIATED WITH LABOR
AND THE PUERPERIUM
CASE 15

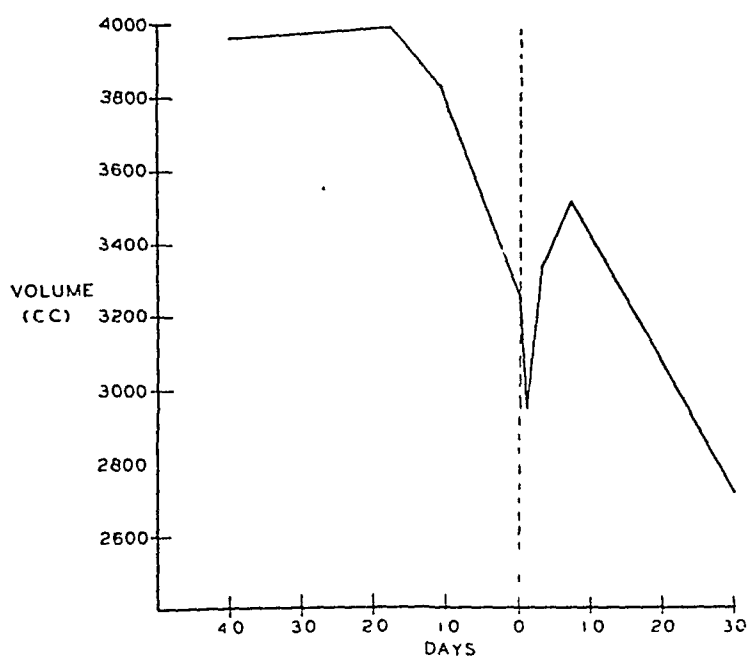


Fig. 2.

TABLE I—CONT'D

CASE NO.	PARITY	WEIGHT IN POUNDS	DAY ANTE PARTUM	DAY POST PARTUM	PLASMA C.C.	VOLUME C.C./KG.	LVHCT*	EXTRA-VASCULAR C.C.	FLUID VOLUME C.C./KG.
16	1	110.5	196		2960	62.0	35.6	11,050	220
		117	161		3290	62.0	34.9	11,500	216
		122.5	120		3420	61.6	34.2	12,680	228
		124.5	78		3525	62.4	32.2	12,400	220
		132	43		3620	60.4	33.5	13,600	225
		137	6		3580	57.5	34.5	15,850	257
		117		45	2665	48.0	37.3	11,650	219
17	2	129.5	200		3580	61.0	36.4	13,900	237
		130	165		3615	61.0	34.1	14,200	240
		139.5	126		4200	66.0	32.3	16,350	254
		148.5	85		4150	65.5	32.3	16,000	238
		151.5	44		4325	63.0	31.5	18,200	270
		155	16		4600	65.0	29.8	20,600	300
		157	4		4560	64.0	28.6	20,500	292
				7	3580		21.2	16,400	229
		136		33	3200	58.0	35.0	13,200	215

*Large vessel hematocrit.

Associated with labor and the first thirty hours following delivery, plasma volume continued to decrease. When measured again on the third and sixth postpartum days, an increase in volume was noted. On the thirtieth day after delivery plasma volume had returned to normal limits for body weight.

Illustrated graphically in Fig. 3 is the mean per cent plasma volume change of these ten patients. This is based on the mean per cent change from the thirtieth day postpartum volume which has been considered as the non-pregnant normal value for these women. When first observed near the end of the first trimester, the plasma volume was higher than the level subsequently observed thirty days following delivery. A progressive increase in volume then continued until the latter part of the ninth lunar month. The largest individual increase was 72 per cent, the lowest was 36 per cent, with an average increase of 49 per cent over the postpartum nonpregnant levels. There was a 25 per cent prelabor decrease of the total increase of plasma volume which had occurred during pregnancy. No relationship was noted during gestation between weight variations and, plasma volume.

Extravascular Fluid.—Repeated simultaneous measurements of plasma and extracellular fluid volumes enable one to study the changes which occur both in the vascular and extravascular compartments. These changes in the extravascular fluid volume during pregnancy are illustrated graphically in Fig. 4, in which each individual case is plotted.

In eight of the ten patients studied, extravascular fluid increased throughout the course of pregnancy and, there was no prelabor decrease observed. It is apparent from a consideration of Table I that Cases 11 and 13 did not adhere to this pattern. Case 11 had only a total weight gain of 8.5 pounds during pregnancy. In this patient there was no significant difference between the earliest and latest prepartum extravascular fluid-volume observations. During the entire puerperium, this patient had only a 10-pound weight loss with little decrease in extravascular fluid volume. Her weight increase was no doubt due to the growth of the products of conception. This absence of extravascular volume changes is in contrast to that of the other nine patients who gained from 20 to 36 pounds and who during pregnancy had more marked changes

in this compartment. This group can be assumed to represent the average pregnant patient whose weight gain is due to both the growth of the conceptus and the storage of water. Case 13 was a patient who had a sudden 13-pound weight gain between the thirty-first and thirty-sixth week of pregnancy. This was associated with an 11 L. increase in extravascular fluid volume. During the next three weeks prior to the onset of labor, there was a 3-pound weight gain with a 5 L. prelabor decrease in extravascular fluid volume. Assuming the determinations to be entirely correct, this suggests a possible shift of fluid from the extravascular to the intracellular space.

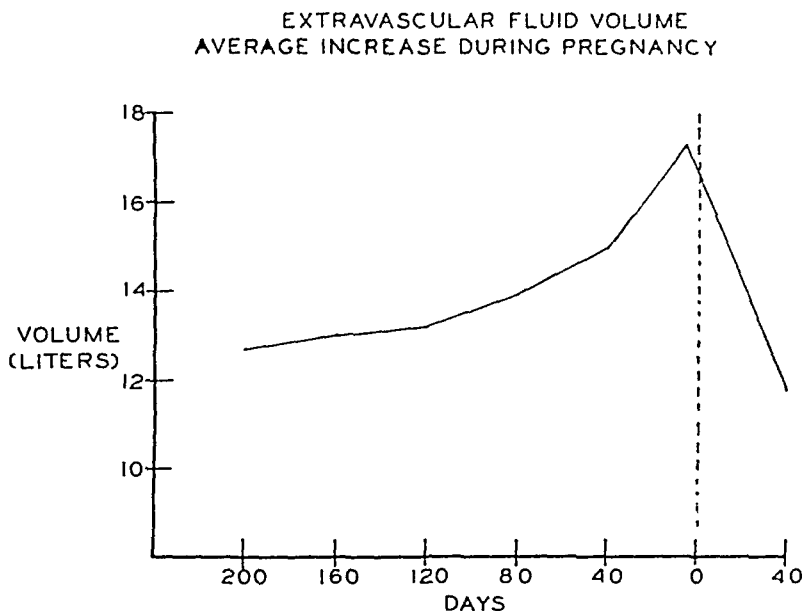


Fig. 5.

In Fig. 5 is illustrated the average extravascular fluid volume for these ten individuals during pregnancy. In the latter part of the first and during the second trimester there was only a slight elevation in the volume of this space, while during the last trimester there was a marked increase. During the period of pregnancy in which the observations were made, there was an average total increase of 4,600 c.c. With the exception of Case 13, the peak volume was reached during the eleven days preceding the onset of labor. In five patients in whom the extravascular fluid volume was measured at the end of the first week in the puerperium, an average decrease of 2,500 c.c. had occurred. The volume of this compartment when measured 26 to 66 days after delivery had decreased 59 per cent from the maximum prepartum increase. These last observations of extravascular fluid volume constituted 19 per cent of body weight which is still greater than the accepted normal nonpregnant value of 15 per cent. This slow decrease in extravascular fluid volume is in contrast to the more rapid return of plasma volume to normal.

Selective Retention of Fluid in Plasma and Extravascular Compartments

The vascular and extravascular spaces, which make up the extracellular fluid compartment, retain fluid at different rates and amounts in each trimester of pregnancy. These data are illustrated graphically in Fig. 6, and show the ratio of the absolute changes in extravascular fluid to plasma volume. A significant change in this ratio is first noted approximately 160 days prior to the

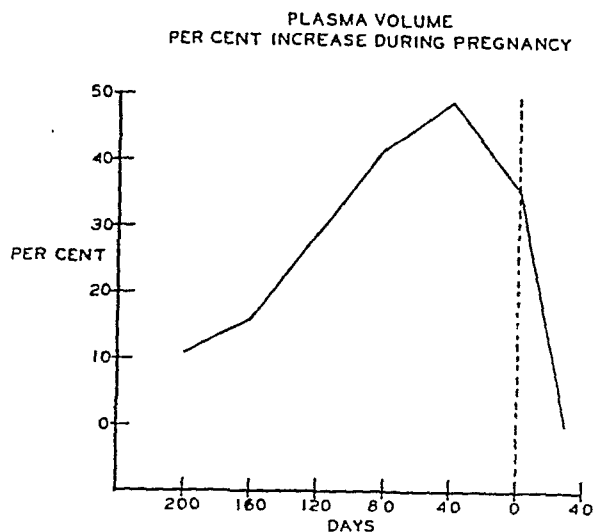


Fig. 3.

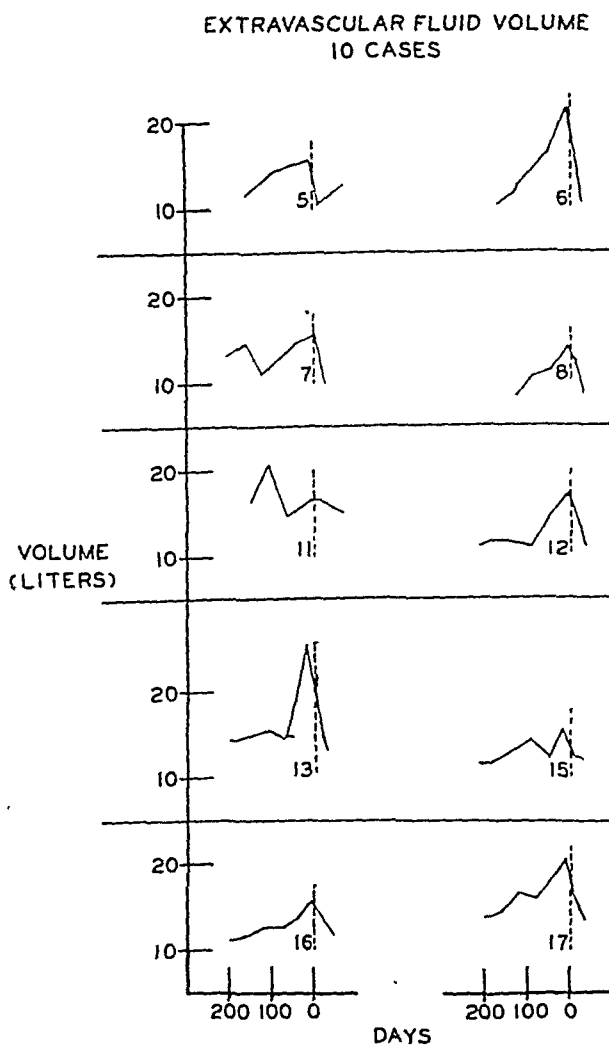


Fig. 4.

That intravenously injected T-1824 does gain access to the lymph has been established. Ferrebee et al.⁸ have measured the amount of dye appearing in the thoracic and cervical lymph of dogs at intervals following injection. In one experiment, 7.5 per cent of the injected dye had appeared in the thoracic lymph in two hours.

Much information can be gained by inspection of the characteristics of the disappearance slopes obtained in the individual plasma-volume determinations. All of the slopes obtained were linear during the sampling period of fifty minutes. In no instance did the dye concentration of individual plasma samples deviate from the general slope of the curve in direction or magnitude sufficient to indicate any recirculation of the dye from the lymphatics into the circulating plasma. Furthermore, the rate of disappearance of the standard quantity of dye injected did not vary by more than 2 per cent in successive determinations in the same individual during the course of pregnancy and the puerperium. The concentration of dye in the initial postinjection sample taken ten minutes later closely approximated the value used in calculating plasma volume. It follows that if an amount of dye sufficient to affect the accuracy of plasma volume determination had entered either the lymph or extracellular fluid compartments, or both, this entry must have occurred during the time in which the dye was becoming mixed in the blood stream, i.e., within the first ten minutes after injection. It would also appear that, if large amounts of dye entered the lymph immediately following the injection, some evidence of the return of lymph-borne dye to the circulating plasma via the thoracic duct would have been found at some time during the sampling period. As stated above, there was nothing in the individual disappearance curves to indicate recirculation of the dye. The results of extravascular fluid volume determinations indicate that there is a continued hydration of this compartment through the last ten days of pregnancy. In the measurements of extravascular fluid volume made in this study, a correction was made according to the method of Crandall and Anderson⁹ for the amount of thiocyanate diffusing into the maternal red cells. A more accurate correction figure was obtained by determining the circulating red-cell mass with red cells tagged with radioactive iron, Fe 55.¹⁰ However, it is not possible to determine with this degree of accuracy the thiocyanate diffusion into the amniotic fluid and the fetal and placental mass. The amniotic fluid reaches a maximum volume of 1,000 c.c. to 1,500 c.c. at the seventh month of pregnancy. Following this peak, there is a steady decline and at term the amount is considered to be less than 700 c.c.¹¹ During this latter phase of gestation there is a progressive increase in fetal mass amounting to approximately 1,600 Gm. The amount of extracellular water in the fetal mass has been determined to lie between 30 per cent and 43 per cent.^{6, 12} This would represent a 500 c.c. to 700 c.c. increase in fetal thiocyanate space in the last eight weeks of pregnancy. It will be readily noted that this fetal increase is offset by the progressive decrease in amniotic fluid volume.

The ratio of the changes between extravascular fluid volume and plasma volume suggest a selective or differential retention of fluid in the extravascular compartment. This selective retention rather than a simple hydration first manifests itself about 160 days prior to the onset of labor. From this time and continuing until the 80th day prior to labor, there is a greater percentage increase in plasma volume than in extravascular fluid. Beginning about the 80th day, extravascular fluid volume increases much more rapidly than plasma volume and this process is further augmented by the prelabor decrease in plasma volume.

onset of labor. Although the volumes of plasma and extravascular fluid are each increasing during the early period of gestation, plasma volume is increasing to a much greater degree than extravascular fluid. This is reflected by a decrease in the ratio between the volumes of the two compartments. The depressed ratio continues through the second and into the first part of the last trimester. Approximately eighty days prior to the onset of labor, there is a marked reversal of the ratio. This change in the ratio is the result of an accelerated increase in extravascular fluid volume which is further augmented by the decrease in plasma volume occurring about the 40th day prior to delivery. At delivery and in the puerperium when checked at seven and thirty days, there is no significant difference in this ratio.

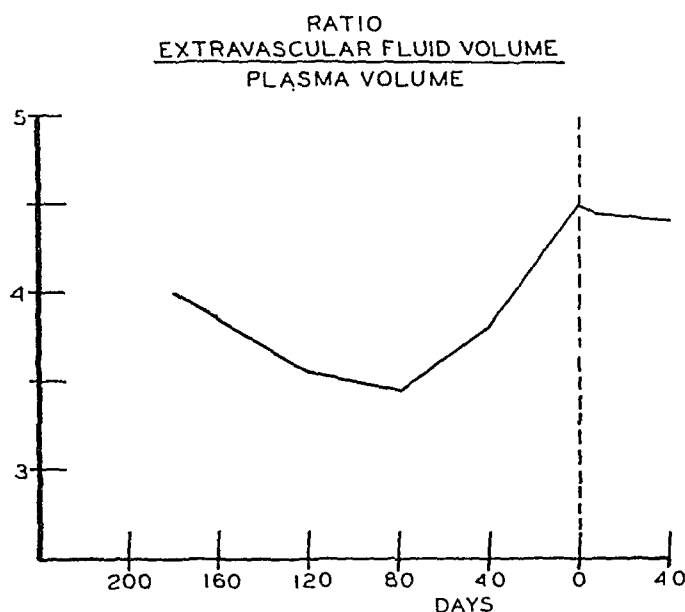


Fig. 6.

Discussion

These studies are in accord with previous observations that there is a marked increase in plasma volume during the course of pregnancy. Furthermore, there is a prelabor decrease in plasma volume. When the average of the last antepartum plasma volume determination in the patients who went to term is subtracted from the average of the highest antepartum observation, the mean difference is -347 c.c. The standard error of the individual differences is 100.2 c.c.; the ratio of the difference between the two means and the standard error of the differences is 3.73, which proves that the prelabor decrease of plasma volume is statistically significant.

The question arises whether the progressive increase in plasma volume as measured by the dye method is a real increase or whether the results obtained are due to unsuspected sources of error in the method used during pregnancy. Since plasma volumes are based on the disappearance slopes of the injected dye, any factor that would lead to admixture of the dye in fluid compartments in which the dye does not gain access in the nonpregnant state might lead to erroneous results. Two alterations in fluid circulation and balance which are known to occur in pregnancy suggest themselves as possible disturbing factors, namely, an increase in the lymph load and a demonstrated increase in extracellular fluid.

CERTAIN ASPECTS OF ECLAMPSIA*

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CONVULSIONS may arise in a woman during her last trimester of gestation from as many different causes as in the nonpregnant female or the male. In addition, the syndrome called eclampsia, characterized by convulsive seizures and other specific signs and symptoms, may occur as a unique complication of late pregnancy.

The etiology of the disease remains unknown, although the number of theories, past and present, proposed to explain its causation is legion. Many of the theories postulated in the past have, at present, only an historical interest. It seems fairly certain now that eclampsia is not due to uremia, bacterial infection, autointoxication, nor to changes in the mammae, nor to edema per se. These theories and others may be discarded because of data which have been accumulated in many hospitals and research institutions.

As a classical example of an outdated theory, the old mammary hypothesis of Sellheim may be cited. This theory was based upon the superficial resemblance between eclampsia and parturient paresis of cattle. We know now that the latter disease in cattle is due entirely to hypoglycemia, and no one today practices mastectomy in the treatment of eclampsia. Unfortunately, the pathogenesis of eclampsia has not been so easy to elucidate.

Even if we do discard many of the older theories which have not been substantiated, we are still left with a rather long list of theories. Since it would be impossible to discuss all these even briefly, we have elected to present a summary of the theories which have been considered in recent years. These have been divided into three main groups, simply for the purpose of classification. There are obviously some injustices in this classification, because certain theories cannot be placed in any particular category; but we hope that the majority of the present-day theories have been included. For a discussion of most of them, we shall be forced to refer you to the several critical reviews of the subject which have appeared in recent years (Browne, 1944, Theobald, 1946, Hofbauer, 1946).

We shall discuss in some detail a few of the theories which hold a particular interest for us. In doing this, we wish to make it clear that we are not attempting to rate any particular theory, based upon adequate data, above or beyond any other theory with an equal amount of data as its background. Furthermore, we are not interested in propounding any particular theory of our own.

*Address presented before the International Congress of Obstetrics and Gynaecology, Dublin, Eyre, July 8, 1947, by the late Dr. Stander.

†Died May 2, 1948.

Conclusions

1. The plasma volume increased markedly during pregnancy and reached maximum volume during the 68th to 5th day prior to the onset of labor. This increase was 49 per cent when compared with the nonpregnant values thirty days following delivery.

2. There was a statistically significant decrease of plasma volume in the latter weeks of pregnancy, averaging 25 per cent of the total increase which had occurred during pregnancy.

3. Plasma volume had returned to normal nonpregnant values by the thirtieth day after delivery.

4. There was an increase in the amount of extravascular fluid up to the onset of labor. The rate of increase was accelerated during the last trimester with no evidence of any prelabor decrease.

5. In the first week of the puerperium there was a 2,500 c.c. decrease in extravascular fluid volume. /

6. The extravascular fluid volume, when measured for the final time between the twenty-sixth and sixty-sixth day of the puerperium, was 59 per cent below the maximum prepartum value.

7. The vascular and extravascular spaces show a retention of fluid which varies in amount in each trimester of pregnancy. During the first and second trimesters, the percentage increase of plasma volume exceeds the percentage increase of extravascular fluid volume. In the last trimester, the percentage increase in extravascular fluid volume is greater than the percentage increase in plasma volume.

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We certainly think data should continue to be collected along these lines. Furthermore, efforts should be made to make the dietary data more quantitative. For instance, a diet may be poor in a number of different ways so all data collected on "poor" diets may not be comparable. We could ask, for example, what would have been the incidence of pre-eclampsia in groups, similar to Burke's "very poor" and "poor" groups, receiving supplements sufficient to make each and every one of their diets excellent. We are planning to carry out some experiments in our own clinic which might or might not shed light upon this phase of the problem. We plan to study the nitrogen and mineral balances of patients to determine, first, what the nitrogen balance is in patients with severe pre-eclampsia and, then, whether any dietary factors might affect that balance.

We shall now discuss briefly some of the theories which consider the primary fault to occur in the maternal organism. We shall not consider the constitutional predisposition or the pressure theories, nor those which ascribe the cause to the dysfunction of one particular endocrine gland. We shall outline briefly the development of one theory, proposed as an endocrine hypothesis and subsequently modified. As you all know, Smith and Smith, in 1934, originally observed the blood and urine chorionic gonadotropins to be higher and the estrogens lower in toxemic than in normal patients. These changes, though similar to those which occur, according to the Smiths, in normal cases at the time of labor, start some weeks before the onset of the symptoms of toxemia. There is also a decreased excretion of pregnandiol. The findings were interpreted as indicating a dysfunction in the metabolism of these hormones which led to the toxemic syndrome.

TABLE II. CAUSES POSTULATED WITHIN MATERNAL ORGANISM

1. Constitutional predisposition
2. Pressure theory
3. Endocrine imbalance
a. Pituitary
b. Adrenal cortex
c. Others
4. Chemical poisons
a. Guanidine
b. Histamine
c. Tyramine

Subsequent work, in general, has borne out the observations of the Smiths with regard to the blood levels and the excretion of the hormones. However, the picture has become rather more obscure than clear as more work is done. The data to date along these lines have been summarized by Rubin, Dorfman, and Miller. In general, there is agreement among all workers that the pregnandiol excretion is decreased. Urine estrogens were not always found low, while serum estrogens, where determined, were low in only about 25 per cent of the cases. Urine and chorionic gonadotropins have not been found elevated in all cases. One group of workers reports serum chorionic gonadotropins within normal limits. Such variations certainly suggest discrepancies, the explanation for which must await more data. To speculate, one might wonder how much of this variation may be due to an altered kidney function.

The Smiths have carried their theory further and have more recently observed a toxic euglobulin to occur in the menstrual discharge. They attribute the local vascular changes seen in menstruation to this substance. A substance of similar activity, as judged by the precipitin test, appears in the blood of menstruating and toxemic women and in pleural exudates. This toxin also seems to have marked fibrinolytic activity associated with it, which may be a separate factor. This enzyme is also present in the euglobulin fraction of the blood, and they postulate that tissue damage from any cause releases a proteolytic enzyme (the fibrinolysin?) which in turn yields a labile toxic protein.

First, let us consider those theories which postulate that the fault lies outside the maternal organism. Those which consider the meteorologic influences will be discussed by others here, and may be omitted from this presentation. We can probably dismiss for now, and possibly forever, those theories which postulate some sort of infection as being the instigator of the eclamptic syndrome.

The theory which postulates that the disease is the sequela of a dietary deficiency, either single or multiple, still deserves attention. This theory was originally propounded here in Dublin, although with a somewhat different interpretation from that of today. Nevertheless, it seems appropriate to consider it first. In recent years, this theory has gained new proponents and has been tested in several ways. Clinical experiments have been conducted in which the diet ordinarily consumed during pregnancy has been supplemented with many dietary factors (Ross et al., 1938, Ebbs, Tisdall, and Scott, 1941, People's League of Health Experiment, 1942). The results in general have not been striking. Only in the League Experiment was there a significant decrease in the number of primiparas who developed albuminuria with or without hypertension and/or pre-eclampsia in the supplemented group.

TABLE I. CAUSES POSTULATED OUTSIDE MATERNAL ORGANISM

1. Dietary deficiency
a. General
b. Protein
c. Calcium
d. Vitamin
2. Infection
a. Pyelitis
b. Septic foci to infect placenta
3. Meteorologic influences

Another approach, made by Burke and her collaborators in 1943, has been to conduct a dietary survey during the last trimester of pregnancy. Her data show that 44 per cent of the patients in the "very poor" and "poor" diet groups developed pre-eclampsia and 8 per cent in the "fair" group. There was no pre-eclampsia in the "good" and "excellent" diet groups. These differences are statistically significant; however, when these findings are analyzed on the basis of protein alone, the relationship between low-protein diet and incidence of toxemia is not significant (Stuart, 1947).

It is Theobald's view (1946) that a deficiency in one or more of several factors might lead to the syndrome we call eclampsia. Theobald states, "The dietetic deficiency hypothesis alone satisfies all eclamptic postulates. The evidence in its favor, and in particular that afforded by the geographic distribution of the toxemias of pregnancy, appears very strong. Nevertheless, its proof awaits the satisfactory demonstration that they can be prevented."

Arnell, Goldman, and Bertucci (1945) have also presented evidence to indicate that protein intake may be related to the development of pre-eclampsia and eclampsia. They do not hold the view, however, that protein deficiency is the "only factor in the causation" of the disease. These and other studies (Strauss, 1938, Holmes, 1941, Bibb, 1941, Theobald, 1946), though not conclusive, suggest that diet may definitely play a role in the development of eclampsia and severe pre-eclampsia. Whether its role is primary or secondary remains to be seen.

The classic criticism of the dietary theory has been the observed decrease in the incidence of eclampsia which occurred in parts of Germany during World War I. A similar decrease in the incidence of eclampsia has been reported to have occurred in Holland in World War II during the "hunger winter" of 1945 (Smith, 1947). Any dietary theory of eclampsia, to be valid, must explain these decreases.

usually something outside the placenta, which is postulated to bring about the change in the placenta. Such a state of affairs shows that we are really ignorant of the actual cause of the disease or the sequence of changes which occur during its development. Theoretically, one can make an excellent case for the placenta's being involved in the development of the disease, and actually this has been done by many writers. You all know of Young's infarct theory and how it has grown to require an X factor which in turn, due possibly to a vitamin deficiency, leads to disturbance of the endocrine metabolism, probably by interfering with the maternal circulation in the placenta (Young, 1942). This in turn leads to the placental infarction, the products of this necrosis eventuating in eclampsia.

Bartholomew (1936) explains the development of the placental infarcts in a different way. The hypercholesterolemia of pregnancy plus a diet rich in cholesterol leads to an excessive storage of cholesterol in the arteries of the placental villi. This storage enhances or predisposes this area to potential infarcts, the actual precipitating factor being fetal movements. Page (1939), as a working hypothesis, considers the placenta to behave as the kidney and that any condition which tends toward uterine ischemia might cause the liberation of a pressor substance from the placenta, much as the kidney liberates a pressor substance after its circulation has been constricted by a Goldblatt clamp. The theory propounded by the Smiths also seems now to go back to the placenta, requiring an alteration in the uterine circulation for the subsequent liberation of a toxin and/or alteration of the hormonal balance. Dexter and Weiss (1941), too, are of the opinion that, "The present evidence points to the placenta as the 'intra-uterine factor' responsible for toxemia of pregnancy. But probably the renal humoral factor of the pre-existing hypertension has a deleterious effect on the placental circulation, enhancing the development of the characteristic degenerative process in the placenta." Dieckmann (1941) likewise considers the placenta as being indirectly responsible for the liver lesions seen in eclampsia. The constant entrance of chorionic tissue fibrinogen from the placenta into the circulation consumes the proteolytic enzymes which normally destroy proteins absorbed from the intestines. The proteins in the portal circulation then cause the liver damage.

TABLE III. CAUSES POSTULATED WITHIN PRODUCTS OF CONCEPTION

A. Placenta	
1.	Infarct
2.	Ischemia
3.	Crush syndrome
4.	Allergy
5.	Elements
B. Fetus	
1.	Endocrine imbalance
	Adrenal cortex
2.	Iso-immunization
a.	Rh factor
b.	Other factors

We are not going to attempt to evaluate these theories. Nor is it worth while trying to determine which one is correct. We are quite willing to concede that the placenta may well be involved in the development of the disease. But the stage at which it becomes involved is still undetermined.

Finally, as far as theories go, we can probably rule out isoimmunization as an etiological factor, since Hurst, Taylor, and Wiener (1946) found no significant difference in the incompatible blood groups in infants or mothers with toxemia from those in mothers without toxemia, and no correlation between toxemia and Rh incompatibility.

Late toxemias of pregnancy, therefore, might be due to a withdrawal of hormonal support resulting in the elaboration of the toxin. The reasons for the withdrawal of the hormonal support seems, in their theory, to be due to an inadequate supply of blood to the placenta. The primary cause of eclampsia, then, becomes any mechanism or factor which interferes with the blood supply of the uterus. The changes from normal which they have observed in the hormonal pattern and the toxin thus apparently become sequelae to the decrease in blood supply. But why does the blood supply decrease?

The hormonal theory, particularly as it relates to the female sex hormones, is attractive and intriguing because there is such a marked change in the concentration of these hormones during pregnancy. However, rather than speculate, let us await more evidence on the normal metabolism of these substances.

Next, we shall consider briefly the histidine hypothesis as an example of the theories which postulate an amine as being responsible for the eclamptic syndrome. As you know, this theory was postulated in 1926 by Hofbauer. It now has a new exponent in Kapeller-Adler, who observed a histidinuria in normal pregnancy (1934). This observation seems to have been amply confirmed. More recently she has observed a histaminuria to accompany the histidinuria in several complications of pregnancy (1941). Subsequently, she reported (1943) a histaminuria accompanying the histidinuria in seven out of ten cases of hyperemesis gravidarum, in three out of ten cases of threatened abortion, and in twelve out of sixteen cases of mild pre-eclampsia. Only traces of histidine and of histamine were found in the urine in ten cases of severe pre-eclampsia and eclampsia. On the basis of these and other data, she postulates that "histidine and histamine play a significant part in normal and toxemic pregnancy." Further, "The fact that histamine has been isolated from the urine of patients suffering from pre-eclamptic toxemias, as well as from urine of women suffering from hyperemesis gravidarum, suggests that pre-eclamptic and eclamptic toxemia, toxemic vomiting, and premature separation of the placenta may not represent independent diseases, but may form only different manifestations of the same disease, probably an intoxication by histamine." The histamine arises, it is assumed, by the dysfunction of histidine decarboxylase and histaminase. These enzymes can be affected by a number of factors, but whether they are or not is another question.

The finding of histidine and histamine in the urine during pregnancy is of interest, but one doubts whether the sweeping generalizations are at all justified from the data in hand. Furthermore, if severe pre-eclampsia and eclampsia are due to histamine, we should expect some amelioration of the symptoms by the antihistamines. If these drugs do lessen the severity of the disease, the histamine theory certainly will be greatly enhanced. But we are still faced with the question of how and where is the histamine produced in excess? We can also ask why the histidinuria of pregnancy? Is it due to an increase in the amount of histidine metabolized or due to an inability of the kidney to reabsorb histidine? Page's data (1946) indicate that the latter might be the case. But if so, why? It is known, for instance, that histidine is not required for the maintenance of nitrogen balance in the adult male (Rose et al., 1943). But is it required by the pregnant female? Does the fetus require it for growth? We can go on asking such specific questions, the answers to which may be obtained by direct experiment in many cases, and when we have enough of these answers we may be able to evaluate more competently the histidinuria and histaminuria of pregnancy and the complications of pregnancy.

Finally, we shall discuss a few aspects of the various theories involving the placenta as the site of the genesis of the eclamptic syndrome. It seems, in the end, that many of the theories do come to involve the placenta, and then there is

As most chemical and metabolic studies on eclampsia have been made only during the height of the disease, we have attempted to obtain blood and urinary determinations prior to the outbreak of the eclampsia. From Table V it will be seen that blood studies were performed five or more days prior to the first convulsion in 23.7 per cent and prior to delivery in 39.5 per cent of the patients. In slightly over one-third of the patients, the first chemical study was made at the time of the convulsion or shortly thereafter.

TABLE VI. AVERAGE BLOOD CHEMISTRY VALUES IN ANTEPARTUM AND INTRAPARTUM ECLAMPSIA, 46 CASES

CONSTITUENT	ON ADMISSION	AT HEIGHT OF DISEASE*	ON DISCHARGE
N. P. N. mg. per cent	32	39	33
Uric acid mg. per cent	4.4	6.6	3.3
Urea N. mg. per cent	12.1	15.9	11.5
CO ₂ vol. per cent	42	43	53
Chlorides mg. per cent (as NaCl)	500	493	489

*As judged by elevation in nonprotein nitrogen and uric acid.

These blood chemical values, as well as those at the height of the disease, are averaged in Table VI. The striking findings are increased nonprotein and urea nitrogen and uric acid. All the values are essentially normal at the time of discharge. Although the carbon dioxide values on admission are close to normal, markedly low figures are seen following the development of convulsions, as shown in the last column of Table VII.

TABLE VII. CARBON DIOXIDE COMBINING POWER IN ECLAMPSIA

TIME OF SPECIMEN	NUMBER OF ANALYSES	AVERAGE CO ₂	RANGE OF CO ₂
Admission	38	42	26-55
24 hrs. AC	18	43	27-54
12 hrs. AC	4	45	37-49
8 hrs. AC	4	33	23-42
4 hrs. AC	—	—	—
2 hrs. AC	2	40	37-43
1 hr. AC	1	49	—
Less than 1 hr. PC	26	33	23-47
1 hr. PC	6	38	28-48
2 hrs. PC	5	45	40-53
4 hrs. PC	5	43	38-47
12 hrs. PC	17	44	34-58
24 hrs. PC	27	45	32-58
Discharge	45	53	46-66

AC—Anteconvulsions

PC—Postconvulsions

The patients who received sodium lactate because of a low CO₂ combining power are not included in this table.

TABLE VIII. UREA CLEARANCE IN EARLY PUERPERIUM FOLLOWING ECLAMPSIA

DAYS FOLLOWING DELIVERY	ANTE- AND INTRAPARTUM		POSTPARTUM	
	NO. CASES	UREA CLEARANCE % OF NORMAL	NO. CASES	UREA CLEARANCE % OF NORMAL
5-8	17	98	4	110
9-12	17	91	9	104
13-16	6	93	4	79
17-24	2	99	2	74
No record	9	—	6	—
Average		94		96
Average of all				95

It seems, then, that there are enough theories. We now need more data, and especially data to explain the small, consistently observed phenomena which occur during eclampsia. Until these can be explained, there is no particular point in trying to determine the over-all picture. We do not mean to imply that such work is not being done in the field, for it is, but more is needed.

Let us cite, as an example of what we mean, the work has been going on in our own laboratories. We have no particular theory of eclampsia, so we are quite willing to go whither the data will take us. We were inclined to believe, at one time, that the hyperuricemia of pregnancy was due to liver damage. But we were able to show, by studying the clearance of uric acid and urea, that the hyperuricemia and the hyperuremia in the majority of cases are due, at least in part, to an altered kidney function. That nitrogen retention does occur can be seen by comparing the blood chemistry values in normal pregnancy (in early labor) with the blood chemistry values obtained on admission upon the cases of antepartum and intrapartum eclampsia. These and other data will be shown in a brief presentation of the more important statistics on 76 eclamptic patients admitted to our hospital during the past fourteen years and will serve to illustrate certain of the more outstanding laboratory findings.

In order that one may interpret properly certain marked changes noted in eclampsia, the average, as well as the lower and upper limits, of the blood chemical values found in normal pregnancy are presented in Table IV. It will be noted that the nonprotein nitrogen and urea nitrogen tend to lower values at term, returning toward normal nonpregnant figures on the third postpartum day. The blood uric acid seems unaffected by normal gestation, while the carbon dioxide combining power reveals the well-substantiated compensated "acidosis" of pregnancy as labor is approached. On the third postpartum day, the alkali reserve, as shown by the carbon dioxide values, is nearing the normal level.

TABLE IV. BLOOD CHEMISTRY VALUES IN NORMAL PREGNANCY

BLOOD CONSTITUENT	EARLY LABOR		THREE DAYS POST PARTUM	
	NUMBER OF CASES	VALUE	NUMBER OF CASES	VALUE
Nonprotein nitrogen	13	23 Limits 20-26	10	28 Limits 24-36
Uric acid	13	3.1 Limits 1.7-4.4	10	3.0 Limits 1.9-5.4
CO ₂ combining power	13	46 Limits 40-51	9	55 Limits 49-60
Urea nitrogen	13	9.0 Limits 6.1-12.0	10	11.7 Limits 8.1-18.6

TABLE V. TIME OF ADMISSION BLOOD CHEMISTRY IN ANTEPARTUM AND INTRAPARTUM ECLAMPSIA

TIME DAYS	ANTEPARTUM		ANTECONVULSION	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
5 or more	15	39.5	9	23.7
4	1	2.6	0	—
3	2	5.3	1	2.6
2	9	23.7	4	10.5
1	3	7.9	8	21.0
0	7	18.4	14	36.9
1	1	2.6	2	5.3
Total	38		38	

TABLE XII. FETAL MORTALITY IN ECLAMPSIA, 22 CASES

TYPE	DELIVERY		TOTAL	PER CENT
	SPONTANEOUS	OPERATIVE		
Macerated	7	2	9	40.9
Deadborn	3	3	6	27.3
Stillborn	1	—	1	4.5
Died*	1	5	6	27.3
Total	12	10	22	100.0

*Within four days of delivery.

Finally, a follow-up study is depicted in Tables XIII and XIV. From these, it would appear that 66 per cent of the patients for whom we have follow-up records have no hypertension six weeks after the cessation of the disease, and only about 15 per cent show a persistent hypertension. Of the 76 eclamptic patients, 19 had subsequent pregnancies, although this is undoubtedly far too low a figure, as most of these patients were not seen after their six-weeks postpartum examination following the eclampsia. However, of the 19 known to us to have had a subsequent pregnancy, two had severe pre-eclampsia and three mild pre-eclampsia in these subsequent pregnancies.

TABLE XIII. SUBSEQUENT COURSE FOLLOWING ECLAMPSIA, 76 TOTAL CASES

SIX WEEKS BLOOD PRESSURE	NUMBER OF CASES	PER CENT
Below 140/90	38	51.3
Above 140/90	20	26.3
No record	18	22.4
Total	76	100.0

20 CASES WITH BLOOD PRESSURE ABOVE 140/90 AT SIX WEEKS POST PARTUM

BLOOD PRESSURE	NUMBER OF CASES	PER CENT
Below 140/90 later	9	45
Stays above 140/90	9	45
No record	2	10

TABLE XIV. SUBSEQUENT OBSTETRIC HISTORY OF ECLAMPTIC PATIENTS, 76 TOTAL CASES

SUBSEQUENT PREGNANCY	NUMBER OF CASES	PER CENT
No record of subsequent pregnancies	57	75.0
One subsequent pregnancy	15	19.7
Two subsequent pregnancies	4	5.3
Total	76	100.0

23 CASES WITH SUBSEQUENT PREGNANCY

COMPLICATION	SUBSEQUENT PREGNANCIES	
	ONE	TWO
No complications	6	3
Severe pre-eclampsia	2	—
Mild pre-eclampsia	2	1
Abortion	1	1
Ectopic	0	1
Deadborn	—	2
No record of outcome	4	—
Total	15	8

The laboratory findings presented above have not taken us very close to the core of the problem; however, we have learned a little about eclampsia and more about the utilization of the blood chemical findings in the treatment of the

In each of the 61 of the 76 antepartum, intrapartum, and postpartum eclamptic patients in whom the urea clearance was determined, the kidney function, as shown by this test, was within normal limits at the time of discharge (Table VIII).

The type of delivery is shown in the following table (Table IX). Twenty-six per cent of the ante- and intrapartum and sixty per cent of the postpartum eclamptic patients had a spontaneous vaginal delivery. Almost half the former group and only 6.7 per cent of the latter had forceps delivery. We were greatly surprised to see the very high incidence of breech delivery, 12 per cent and 19 per cent in the ante- and intrapartum, and postpartum, groups, respectively. Cesarean section was performed in a relatively small number of these patients, 14 and 3.8 per cent, respectively, in the two groups. It is also interesting to note that four of the 26 patients with postpartum eclampsia had twins.

TABLE IX. TYPE OF DELIVERY IN ECLAMPSIA, 76 CASES

TYPE OF DELIVERY	ANTE- AND INTRAPARTUM		POSTPARTUM	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
Spontaneous	13	26.0	18	69.2
Operative:				
Forceps	24	48.0	2	7.7
Breech	6	12.0	5	19.3
Section	7	14.0	1	3.8
Total	50	100.0	26*	100.0

*Four of these 26 patients had twin pregnancies and in each case the second twin presented by breech.

In the 68 patients with vaginal delivery, labor was induced in 38.3 per cent (Table X).

TABLE X. TYPE OF INDUCTION IN ECLAMPTIC PATIENTS WITH VAGINAL DELIVERIES, 68 CASES

TYPE OF INDUCTION	NUMBER OF CASES	PER CENT
Medical	11 ¹	16.2
Rupture of membranes	8 ²	11.8
Bag	5	7.4
Bougie	2	2.9
Total	26	38.3

¹Includes one postpartum case.

²Includes three postpartum cases.

The maternal and fetal mortalities are shown in Table XI. The uncorrected maternal mortality was 1.3 per cent and the gross fetal 29 per cent. The latter group is further analyzed in Table XII, which shows the great majority to have been macerated or deadborn.

TABLE XI. MATERNAL AND FETAL MORTALITY IN ECLAMPSIA, 76 CASES

TYPE OF DELIVERY	MATERNAL MORTALITY		FETAL MORTALITY	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
Spontaneous	—	—	12	15.8
Operative	1*	1.3	10	13.2
Total	1	1.3	22	29.0

*Low forceps.

THE TREATMENT OF ADVANCED CARCINOMA OF THE OVARY*

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IN A previous paper, one of us (E. V. H.)¹ reported a survey of one hundred cases of cancer of the ovary treated by eighteen surgeons on the gynecologic services of the Elizabeth Steel Magee and the St. Francis Hospitals, Pittsburgh, Pennsylvania. Thirty-seven of these cases were on the service of the senior author.

The cases were classified clinically as follows:

Group I.—The tumor is completely removable and is apparently confined entirely to the ovary.

Group II.—The tumor is completely removable but with adhesions or involvement of other structures that can be removed.

Group III.—The tumor is only partly removable on account of extension to other structures.

Group IV.—The tumor is irremovable because of extensive involvement of adjacent parts, and only a biopsy is feasible at operation.

In seventy-six of the cases an attempt was made to remove the primary growth and variable amounts of the metastatic growth. In a follow-up study of a hundred patients, sixty-five of them were traced from admission to the hospital to ten and two-thirds years after operation. Thirteen cases are alive from one and one-fourth years to ten and two-thirds years after operation, but to date only four survived five years or more.

With results such as these the question may be asked, why operate on these patients? It is the purpose of this paper to answer this question from our experience with operation alone or operation followed by x-ray therapy.

We believe that operation is indicated:

1. To definitely establish the diagnosis and extent of the disease. (Tuberculous peritonitis, endometrial nodules in the cul-de-sac, nodular chocolate cysts of the ovary, or benign tumors with ascites may simulate ovarian cancer.)

2. In Groups I and II, because there is a probability that all of the malignant growth can be removed.

3. In Group III the cancer is no longer confined to the ovary, but has spread to the viscera and parietal peritoneum and often the omentum, and is frequently associated with ascites. One of the chief purposes of this paper is to discuss the treatment of this group. The condition is 100 per cent fatal if allowed to run its course without operation. X-ray therapy alone has not been curative. When the disease has advanced to the stage where the diagnosis of clinical Group III

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disease. Furthermore, as a by-product, we have learned something about kidney function, because the clearance studies revealed a competition between diodrast and uric acid, which has been of value in studying kidney tubular function. By continuing these studies, we hope we shall be able to follow a path which will lead us nearer to the solution of the problem.

There are many such paths which need studying. Some of them are and have been receiving attention; others not, possibly because our knowledge of physiology is still limited in this particular field.

In conclusion, may we say that the etiology of eclampsia, although unknown at present, should be discoverable by the application of the scientific method. A theory of eclampsia should be, then, a working hypothesis to be tested by experiment.

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Operation.—August 8, 1933. Removal of cervical polyp, cauterization of the cervix, laparotomy and removal of a large quantity of fluid from abdomen. A cystic intraligamentous left ovary about 15 cm. in diameter and a similar cyst on the right side about 8 cm. in diameter were removed. There were nodules on the peritoneum and intestines, and much of the omentum was involved. A large portion of the omentum was excised. Six gauze drains and a sheet of gutta percha were placed over the raw surfaces in the pelvis. Six hundred cubic centimeters of whole blood were given during the operation. *Diagnosis.*—Papilocystadenoma malignum of ovaries, and secondary papillary cystadenoma malignum of peritoneum and omentum. Patient made a good recovery and was seen last in June, 1937, four years after operation. She had been carrying on her vocation as a midwife until that time. She stated then that her abdomen seemed larger and that she was losing weight. On examination no evidence of fluid or tumor was made out and a note was made that the patient "looks as though she should have recurrence of growth, but no evidence is felt except an adherent uterus, and the abdomen seems to be in remarkably good condition considering what was found and what was left at time of operation." In the follow-up in 1945 we learned that she is dead, but we could not learn how long she lived after our last examination, four years after operation. *NOTE.*—Patient had no recurrence of fluid in abdomen or chest and was able to carry on her work as a midwife for at least four years.

CASE 3.—Mrs. M. K., aged 50 years, St. Francis Hospital No. 46,571, was admitted April 12, 1942. *Diagnosis.*—Papilocystadenocarcinoma of the right ovary with generalized abdominal carcinomatosis. *Symptoms.*—Abdominal enlargement and pain. She had had multiple operations in the past on the kidneys, gall-bladder, and had had appendectomy and bilateral salpingectomy. The abdomen had been tapped on several occasions before her present admission to the Hospital. On examination a firm, irregular mass filled the lower abdomen to the level of the umbilicus, and there was marked ascites present. A cystic feeling, fixed mass was present in the cul-de-sac. *Operation.*—April 16, 1942. Approximately 4,000 c.c. of slightly blood tinged fluid was evacuated from the peritoneal cavity. On exposing the mass, a large gray-white, fungating, friable surface was found. The mass was adherent to the pelvic structures and particularly to the uterus and small intestines. Peritoneal implants were present over much of the abdomen. The mass was separated and removed with difficulty. It seemed to arise from the right ovary. Five gauze drains and a sheet of gutta percha were placed over the operative field. Five hundred fifty c.c. of whole blood were given during the operation. *Pathologic Diagnosis.*—Papilopseudomucinous cystadenocarcinoma of the ovary. X-ray therapy was started three weeks after operation. On June 30, 1942, the patient was getting along satisfactorily. A movable nodule was felt in the cul-de-sac, but no masses or fluid were detected in the abdomen. On July 22, 1943, the patient was getting along fairly well. She complained of inability to gain strength, but she looked better. The mass in the cul-de-sac seemed somewhat larger, but there was no evidence of fluid in the abdomen. In answer to the follow-up letter in January, 1945, she wrote that she had some abdominal pain but was able to be up and about and do housework, and tapping had not been necessary since before operation. On April 18, 1945, she was seen at the Tumor Clinic and the following note made: "The patient has only one complaint and that is of intestinal cramps when her bowels move or after taking a laxative. She has gained weight and feels quite well generally. No palpable masses in the abdomen. Considerable thickening of the skin and many hemangiectases of the skin over the lower abdomen which is a postradiation effect." *NOTE.*—Patient has been able to carry on her home duties for three years with no recurrence of ascites, although she had been tapped several times before operation.

CASE 4.—Mrs. J. S., aged 42 years, St. Francis Medical No. 88,008, was admitted Jan. 29, 1944. *Diagnosis.*—Papillary cystadenocarcinoma of both ovaries, ascites. *Complaints.*—Feeling of heaviness and enlargement of the abdomen of one month's duration, and flatulence. Patient menstruated regularly and normally. No history of pregnancies. On examination

can be made, the patient is doomed to a most uncomfortable, semi-invalid or invalid existence for her remaining days. Any salvage of life in this group is very unusual but it may occur and constitutes a surgical triumph.

For a long time there has been an impression that removal of the primary ovarian growths in the presence of metastatic nodules on the peritoneum may prolong the life of the patient, and in a few cases may result in disappearance of the outlying implants. We are not too much interested in the prolongation of life in patients with malignant disease unless it is accompanied by a reasonable degree of comfort to the patient and a life of usefulness.

In the following group of cases, the first case may indicate that life has been saved. In the remainder, the patients have been entirely or at least reasonably comfortable and they have been able to carry on a life of usefulness for a limited time in contrast to the life of invalidism which confronted them when they first appeared for examination. They came to us because of pain and/or enlargement of the abdomen.

Case Reports

CASE 1.—S. R. K., single, aged 49 years, St. Francis Hospital Gynecological No. 35-263, was admitted June 19, 1935. *Diagnosis.*—Papillary adenocarcinoma of the left ovary with metastases to the peritoneum, left broad ligament, and sigmoid colon. *Chief Complaints.*—Pain on defecation (two months), watery stools (two to three years), and abdominal enlargement of one week's duration. She had a normal menstrual history, except three months of amenorrhea recently followed by a menstrual period for three days and then spotting for three weeks. The abdomen was enlarged, and an irregular lobulated mass was felt reaching to the umbilicus. There was evidence of free fluid in the peritoneal cavity. A barium enema revealed no intrinsic lesion in the colon.

Operation.—June 22, 1935. Cauterization of the cervix, supravaginal hysterectomy, bilateral salpingo-oophorectomy. There was a large quantity of bloody fluid in the abdomen. There was a large papillary cystadenocarcinoma of the left ovary which was partly intraligamentous. The sigmoid colon was adherent over it. Masses of carcinoma had broken through the capsule into the broad ligament and were scooped out with the hand, leaving carcinomatous tissue on the sigmoid and in the broad ligament. The right ovary seemed normal. No lesions of the colon or stomach were found. Three gauze drains covered with a sheet of gutta percha were placed over the operative field and brought out through the lower end of the incision. Six hundred fifty cubic centimeters of whole blood were given during the operation. *Diagnosis.*—Papillary cystadenoma malignum of the ovary. Following the operation x-ray therapy was given over the lower abdomen. On Oct. 2, 1935, the patient felt well and was gaining in weight, a small mass was felt in the left side of the cul-de-sac. On Feb. 8, 1936, the patient looked well and had gained 20 pounds in weight. When seen in 1945 she had been teaching school since one year after operation and felt well. There was no evidence of extension of the growth over this span of ten years.

CASE 2.—Mrs. M. Z., aged 48 years, St. Francis Hospital Gynecological No. 33-279, was admitted on July 31, 1933. *Diagnosis.*—Cervical polyp, intraligamentous papillary cystadenoma malignum of ovaries with metastases. *Symptoms.*—Bleeding from rectum for ten days, loss of weight in the last six months, fullness of abdomen, and mass felt in abdomen. Patient ceased menstruating six months ago but with occasional spotting since then. She has had one child and two miscarriages. There was a firm mass in the pelvis extending to above the level of the umbilicus in the left side. There was evidence of free fluid in the abdomen. A small polyp protruded from the cervix. The above mass felt cystic, and small nodular masses were present in the cul-de-sac. There were signs of fluid in the left chest, and the chest was tapped and 900 c.c. of clear yellowish fluid were removed (Meig's syndrome). The next day this was repeated and 1,350 c.c. of fluid were removed.

lower quadrant. On vaginal examination the uterus was found small and pushed forward, and there was a mass in the right side and behind the uterus that was firm, nodular, and fixed, and about 15 cm. in diameter. At operation on Aug. 23, 1944, both ovaries were found much enlarged and nodular. Large fungating, granular masses extended through the capsules of both ovaries and involved the surrounding structures. Small nodules were scattered over the uterus, bladder peritoneum, cul-de-sac, sigmoid colon, appendix, and a few in the omentum. No involvement of the upper abdomen was made out. Hysterectomy and bilateral oophorectomy were carried out. Three gauze drains covered by a gutta percha drain were placed over the raw surfaces in the pelvis. *Pathologic diagnosis.*—Papillary cystadenocarcinoma of ovaries. Deep x-ray therapy was started before the patient left the hospital, and was continued later with the patient ambulant. She had arranged to be married on Oct. 1, 1944, and this plan was discouraged, although she was not told about her true condition. Her fiancé in the Armed Forces was told about her condition, and he insisted on going through with their plans in order that he might turn over his allotment to her when he was overseas, and they were married. On Feb. 5, 1945, the patient felt quite well, had gained in weight; a nodule was palpable in the cul-de-sac. On May 5, 1945, the patient looked well and felt well, she continued to gain in weight and accepted a clerical position and was working daily. The nodule in the cul-de-sac seemed unchanged.

CASE 7.—Mrs. E. P., aged 31 years, Elizabeth Steel Magee Hospital, No. 455, was admitted on Oct. 12, 1935. *Diagnosis.*—Papillary cystadenocarcinoma of the ovary with extension to the peritoneum, omentum, and intestines. *Symptoms.*—Tenderness and pain in the lower abdomen. A mass in the abdomen had been noticed for three weeks. Normal menstrual history except that some clots were passed in the last three months. One child 7 years old. Patient has felt tired recently, and three weeks ago noticed a mass in the lower abdomen. A hard, nodular mass was present in the lower abdomen, reaching for three fingerbreadths' above the pubis. At operation on Oct. 14, 1935, about 500 c.c. of straw-colored fluid, containing flakes of fibrin, was found in the peritoneal cavity. Numerous nodules were present in the omentum. The pelvic organs were matted together in a solid, cancerous growth involving both ovaries, the peritoneum, and intestines. Nodules were felt under the diaphragm. The uterus, both ovaries, and the omentum were removed. Five gauze drains and a sheet of gutta percha were placed over the raw surfaces in the pelvis. *Pathologic diagnosis.*—Adenocarcinoma of both ovaries with extension to the uterine surface and omentum.

The patient had postoperative x-ray therapy. On March 5, 1936, a note was made that the patient looked well and felt well, she drove her own car and had been skiing with her husband. She expected to leave for Florida in three weeks. On examination a nodule 2 cm. in diameter was felt on the right side of the cul-de-sac.

July 23, 1936.—The patient felt well and had gained in weight, pelvic examination as before.

April 7, 1937.—The patient felt well and had returned from her second trip to Florida where she spent three months. She was to take another course of x-ray treatments.

Nov. 17, 1937.—The patient felt well. She was eating and sleeping well, and her weight was increasing. The nodule in the cul-de-sac remained the same.

March 7, 1938.—Patient returned with a history of passing some blood in the urine. She has lost weight recently. On examination there was induration on both sides of the cul-de-sac and evidence of fluid in the abdomen. The patient died on April 4, 1938. NOTE.—This patient lived in comfort and carried on her usual activities for more than two years after operation.

CASE 8.—Mrs. C. S., aged 45 years, Elizabeth Steel Magee Hospital, No. 35,427, was admitted on April 24, 1938. *Diagnosis.*—Papillary cystadenocarcinoma of the left ovary with extension to the peritoneum and intestines. *Complaints.*—Pain in the left lower quadrant and left leg—severe, of one week's duration; loss of weight for three months; and nausea and

the abdomen was enlarged and there was a distinct fluid wave present. The right ovary was cystic and about 5 cm. in diameter, and the left ovary was about 12 cm. in diameter. *Operation.*—February 8, 1944. Papillary growths were found on the external surface of the right ovary. No papillary growths were seen on the left ovary, but on opening it after operation the internal wall of the cyst was covered with papillomatous growths, and some areas of the walls seemed solid. The omentum was studded with papillary growths, and there was a large quantity of reddish-brown fluid in the peritoneal cavity. Total hysterectomy, bilateral salpingo-oophorectomy, and resection of the omentum were done, and gauze drains were placed in the pelvis and carried out through the vagina. On March 1, 1945, the patient felt well and had been carrying on her usual activities. No evidence of fluid or nodules was made out on abdominal and pelvic examination. *NOTE.*—This patient has been restored to normal for thirteen months and there is no evidence of recurrence.

CASE 5.—Miss A. H., aged 42 years, Elizabeth Steel Magee Hospital, No. 32129, was admitted on July 8, 1937. *Diagnosis.*—Papillary cystadenocarcinoma of both ovaries. Complained of a sense of weight and pressure in the bladder for six months. A mass in the abdomen had been noticed for three weeks. Menstrual periods occurred every three weeks in the last two years, and they lasted from seven to ten days. There was a smooth, rounded, slightly tender, somewhat movable tumor felt in the lower abdomen extending for three fingerbreadths above the umbilicus. On vaginal examination with one finger, several nodules were felt beneath the tumor, and the base of the tumor felt fixed. *Operation.*—July 9, 1937. Both ovaries were replaced by masses of papillomatous, friable growth that extended on to the uterus and pelvic peritoneum and fixed the genitals to the surrounding structures. The omentum contained many papillomatous masses. The removal of the pelvic organs was difficult due to obliteration of the landmarks. Bilateral salpingo-oophorectomy, supravaginal hysterectomy, and resection of the omentum was done. Five gauze drains were placed so as to cover the remaining oozing carcinomatous operative field. They were covered with a piece of gutta percha and the drains were brought out of the lower end of the incision. Ovarian masses measured approximately 7 by 10 cm. each and contained very little tissue that could be identified as ovary. *Diagnosis.*—Papillary cystadenocarcinoma of both ovaries with extension to the uterine wall and omentum. Patient made a good recovery and returned to her vocation as schoolteacher in September, 1937. On vaginal examination small residual masses were felt in each adnexal region. On Dec. 27, 1938, one and one-half years after operation, the patient returned complaining of cramps in the left lower quadrant, and flatulence of three days' duration. There was vomiting, and the patient stated that the bowel movements had been getting smaller. A freely movable mass, about 3 cm. in diameter, was felt in the left lower quadrant, presumably in the sigmoid colon, and barium enema revealed a constriction in the sigmoid colon. The signs of partial intestinal obstruction subsided, and the patient was given a course of x-ray therapy. The mass in the left lower quadrant became smaller until it was barely palpable and the patient felt well. The masses in the cul-de-sac remained the same. She resumed teaching in September, 1939. Because of some jagging pains at times in the right lower quadrant, another course of x-ray therapy was given in the Fall of 1939 and again in the Spring of 1940, when the pelvic masses seemed larger. She resumed her teaching following this treatment. On Aug. 12, 1940, she was admitted to the Hospital because of partial intestinal obstruction, and on Aug. 23, 1940, a colostomy was performed. She went home on Sept. 22, 1940, and died on Aug. 14, 1941. *NOTE.*—Except for one episode of partial intestinal obstruction for a few days, the patient was comfortable for three years. She had three courses of x-ray therapy because of residual masses in the pelvis, but was able to carry on as a schoolteacher. Three years after her original operation a colostomy was necessary because of intestinal obstruction. She lived another year but not in comfort or as a useful citizen.

CASE 6.—Miss A. G., aged 21 years, Elizabeth Steel Magee Hospital, No. 64933, was admitted on Aug. 21, 1944. *Diagnosis.*—Papillary cystadenocarcinoma of both ovaries. *Complaints.*—Pain in right side off and on for three years, and lump in the right side noticed recently. Menstrual history normal. A nodular, tender mass was visible and palpable in the right

The patient was a thin emaciated woman who looked anemic and who weighed 96 pounds. Red blood cells, 3,310,000, and hemoglobin 60 per cent. There was a firm, fixed mass in the pelvis reaching to the umbilicus, and which pushed the uterus forward. No nodules were felt, but the mass was fixed. *Operation*.—May 1, 1935. Cauterization of the cervix, bilateral salpingo-oophorectomy. The omentum was adherent over a pelvic mass, and about 100 c.c. of serosanguineous fluid was found in the peritoneal cavity. A large, irregular mass about 20 cm. in diameter replaced the right ovary, and a loop of ileum was adherent to it. The mass was ruptured, and friable tissue escaped in separating the adhesions. The left ovary seemed negative. Four gauze drains and one sheet of gutta percha were placed over the operative site. At the hepatic flexure of the colon was a hard, irregular movable mass about 7 cm. in diameter and involved the whole circumference of the colon. No enlarged glands were felt, and no nodules were detected in the liver. The patient was given 1,200 c.c. of whole blood during the operation. *Pathologic report*.—Adenocarcinoma of the ovary and Fallopian tube. At a second operation on May 22, 1935, the terminal ileum, cecum, ascending colon, hepatic flexure, and one-third of the transverse colon were resected, and ileo-colostomy done. A blood transfusion of 1,200 c.c. was given during operation. *Pathologic report*.—Adenocarcinoma of the colon. The patient made a satisfactory recovery from both operations and was discharged on June 12, 1935, with a red blood count of 3,850,000, and hemoglobin of 86 per cent. On Oct. 14, 1935, patient had gained in weight and had been doing her own housework, but there was a cystic mass in the cul-de-sac which was aspirated and bloody fluid obtained. X-ray therapy was given, and the bowels were loose.

January 9, 1936.—Diarrhea continued, and the patient had lost weight. She died on March 8, 1936, thirteen months after operation.

In the above ten cases, the average survival time has been three years and one month. (This survey was completed in June, 1945.) In January, 1948, thirty-one months later, Cases 1, 3, 4, and 6 are known to be still alive and comfortable.

The following two cases are suggestive, but do not necessarily indicate that the poor results were obtained because operation was not followed by radiation therapy.

CASE 11.—Mrs. S. M., a 42-year-old, thin, white woman was admitted to the Elizabeth Steel Magee Hospital on April 2, 1944, with a chief complaint of lower abdominal pain and backache. The pain dated from 1942, at which time she gave birth to a stillborn ancephalic monster. This had been her only pregnancy. Before the present admission she had nausea and vomiting for two months. A mass was found in the left lower quadrant. A diagnosis of left ovarian cyst with adhesions was made. At operation the cyst was adherent to the sigmoid, and a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done. *Pathologic diagnosis*.—Papillary cystadenocarcinoma of ovary. She was advised to return for x-ray therapy, but failed to do so. She returned to the Hospital with malignant invasion of the bladder and rectum, and died on March 14, 1945, less than twelve months after operation.

CASE 12.—Mrs. M. M., a 56-year-old, well-nourished white woman, the mother of ten children, was admitted to the Elizabeth Steel Magee Hospital on July 17, 1943, complaining of a tender mass in the left lower quadrant. The menopause had occurred fourteen years before, and there had been no vaginal bleeding since then. For three months prior to admission there was difficulty in getting her bowels to move. There was no loss of weight. A left ovarian cyst was found, and operation advised. On opening the abdomen a cyst about 15 cm. in diameter was found adherent to the parietal peritoneum. None of the other pelvic structures was grossly involved. Malignancy was not expected from the gross appearance, and simple removal of the cyst was performed. *Pathologic diagnosis*.—Multilocular papillary cystadenocarcinoma of the ovary. The patient was advised to return for x-ray therapy but refused. She died on April 4, 1945, less than nine months after operation.

vomiting for one month. She menstruated regularly, was pale, and had a sallow color. Hemoglobin was 62 per cent. The uterus was displaced to the right by a mass in the left adnexal region about 8 cm. in diameter. It was not very tender, but the mobility was limited. Impression—malignant growth of the left ovary. Patient had an operation in another city in 1936, and it was learned that at that time she had an adherent papillomatous cyst of the right ovary, and that the appendix and right ovary had been removed and the diagnosis of cyst of the right ovary with intracystic papillomas, nonmalignant, had been made. At operation on May 4, 1938, we found a large papillomatous cyst of the left ovary adherent to the sigmoid and small intestine. In the region where the right ovary had been removed there was a mass of carcinomatous tissue about 4 cm. in diameter. As much of this tissue as seemed feasible was removed, along with the uterus and left ovary. There was no evidence of tumor in the upper abdomen. Gauze drains were placed against the oozing surfaces where malignant tissue had been removed, and they were covered with gutta percha. Blood transfusion was given during the operation. *Pathologic diagnosis.*—Papillary cystadenocarcinoma of the ovary. X-ray therapy was started while the patient was in the hospital, and it was continued later with the patient ambulant. She was completely relieved of the pain in the left lower quadrant and down the left leg.

In November, 1940, the patient was still feeling well and had gained thirty pounds in weight. Three months later she developed edema of the abdominal wall and the legs, and she died two months later. *NOTE.*—This patient had complete relief from pain for two and one-half years after operation and x-ray treatment, and was able to carry on her usual activities.

CASE 9.—Mrs. G. G., aged 43 years, Elizabeth Steel Magee Hospital, No. 60238, was admitted on Aug. 17, 1943. *Diagnosis.*—Papillary cystadenocarcinoma of the ovaries with extension to the peritoneum and broad ligaments. She complained of pain and enlargement in the lower abdomen for the past two months, and frequent menstruation (every two weeks). She had a normal menstrual history until two months ago. She had no children, but had had one miscarriage. There was a tense, cystic, moderately tender mass visible and palpable in the lower abdomen, and it extended up to the umbilicus. The uterus was pushed forward by the mass. No nodules were felt, but the tumor was adherent. At operation on Aug. 18, 1943, a large, cystic left ovary was filled with a brown fluid. The left ovary and right adnexa were adherent and the adhesions of the left ovary to the colon were indurated with tumor tissue. There were nodules scattered over the peritoneum of the uterus and anterior cul-de-sac and in the broad ligaments. A total hysterectomy and bilateral salpingo-oophorectomy were done. The oozing surfaces in the pelvis were covered with gauze drains which were carried down into the vagina. *Pathologic diagnosis.*—Papillary cystadenocarcinoma of the ovary (mesonephroma type). On Sept. 3, 1943, x-ray therapy was started.

June 12, 1945.—The patient was symptom free and vaginal examinations were negative for nodules. Three weeks before the patient began to have pain in the left lower quadrant and shortly afterward she noticed swelling of the left leg. On examination there was tenderness and induration in the region of the left brim of the pelvis and along the left pelvic wall. The vault of the vagina was healed and pliable, and no other masses were felt. Another course of x-ray therapy was given. *NOTE.*—This patient has been free of symptoms and has been able to carry on her usual activities for practically two years, she is now under treatment again with x-ray.

CASE 10.—Mrs. G. P., aged 43 years, St. Francis Hospital Gynecological No. 35-186, was admitted on April 26, 1935. *Diagnosis.*—Secondary adenocarcinoma of the ovary; adenocarcinoma of the hepatic flexure of the colon. *Symptoms.*—Cramps in lower abdomen and diarrhea for eight weeks, and loss of weight. She had a normal menstrual history, except for slight bleeding every two days for the last month. She had had two children. She had lost 15 pounds of weight in the last two months.

The frequency of secondary carcinoma in the ovary has led us to explore the gastrointestinal tract for a primary growth, in all cases of carcinoma of the ovary. The results in carcinoma of the ovary, when it is secondary to carcinoma of the gastrointestinal tract, have been poor as to cure or length of life, because the ovarian carcinoma is already a metastasis from a primary growth. It is in the papillo-cystadenocarcinoma group that operation followed by x-ray therapy seems to increase the duration of life and the comfort of the patient.

In some cases, after operation, when the residual tumor grew and caused pain again, decrease in the size of the tumor and relief of pain followed repetition of x-ray therapy (Cases 5 and 9). Because of these observations, it is felt that x-ray therapy probably prolongs the life of the patient to some extent.

We share the pessimism of most operators in regard to the final results in Group III cases, but do not agree with the practice of some in opening and closing the abdomen without attempting the removal of the primary growth when the disease has spread beyond the ovary.

Reference

1. Helsel, E. V.: AM. J. OBST. & GYNEC. 52: 435, 1946.

A third case illustrates the futility of radiation therapy in advanced cases where it is not feasible to remove the tumor.

CASE 13.—Mrs. N. F., a 54-year-old, robust, white woman was admitted to the Elizabeth Steel Magee Hospital on April 30, 1945, with a chief complaint of lower abdominal pain, associated with frequency of urination and difficulty in defecating. Cystoscopic examination revealed invasion of the bladder wall, and proctoscopic examination revealed marked narrowing of the lumen of the colon. On pelvic examination there was a fixed irregular mass filling the entire left side of the pelvis. Operation was not advised, and radiation therapy was started. This was soon discontinued on account of the marked reaction. The patient became worse rapidly and died on May 27, 1945, twenty-seven days after admission. In addition to this case, two others were studied in which radiation therapy alone was given, the cases being too far advanced to undergo operation. Both failed to improve and were dead within two months of admission.

Discussion

Nine of the above twelve cases which were operated upon were from 42 to 50 years of age. One patient was 56 years old. The other two were 21 and 31 years of age, respectively (Cases 6 and 7), and they lived the normal life of a young woman for a limited time. In Case 6 the patient is still alive and apparently well in 1948.

In some of these cases, removal of the primary growths at first seemed surgically impossible without causing the death of the patient. With careful evaluation of how much operative work the patient could stand and with care in determining the proper lines of cleavage, it was possible to remove the primary tumors, and often masses of outlying growth were scooped out with the hand, leaving behind irremovable malignant tissue. Usually hemorrhage is not severe when working through this type of tissue, and with the aid of blood transfusions during the operation, the primary operative mortality in our own personal series has been low. It is our practice at the end of such operations to cover the operative field in the pelvis with gauze drains over which is placed a sheet of gutta serena. This quickly controls oozing, and the field is walled off by adhesions early and prevents unimpeded extension of the disease through the peritoneal cavity. The gauze drains are removed under light anesthesia in one week.

When there is ascites present, and at times tapping is required frequently, if there is much involvement of the omentum, resection of the involved omentum may eliminate the ascites or greatly prolong the intervals between tapping. In Cases 2, 3, 4, and 5, there was no recurrence of the ascites. In Groups I and II, total hysterectomy and removal of both adnexa should be done whether the disease is unilateral or bilateral. In Group III, the tumor is not completely removable, and this procedure is modified according to conditions, and supravaginal instead of total hysterectomy is usually done. As stated before, the Group III patients have tolerated these extensive operative procedures quite well, the primary mortality has been low, and we are willing to accept a low primary mortality in order to accomplish the results reported. In the Group IV cases, exploratory laparotomy and biopsy alone cannot be done with impunity, as deaths have occurred following this procedure. A careful evaluation of the patient's condition must be made in all cases in order to determine the feasibility and extent of the operative procedure.

as well as in males.¹ Progesterin has also been shown to induce some hyperemia of the area. However, it is noteworthy that, given simultaneously, progesterin inhibits the effects of estrogen on the sexual skin.¹⁴ Once estrogen has stimulated the area, the response is diminished noticeably by the fifth or sixth day after the administration of progesterin. If the two hormones are continued, involution of the sexual skin is induced by the fifteenth or twentieth day, which may resemble that of the ovariectomized animal. Under some experimental conditions, progesterin appears to *modify* rather than simply to *antagonize* the action of estrogen.²

Skin reactivity in monkeys is not absolutely limited to the area of the sexual skin. Bachman et al.,⁴ by giving extraordinary doses of estrogen, have caused a reaction beyond the usual confines of the sexual skin, as well as a redness of the face. Likewise, Hisaw, Greep, and Fevold¹⁴ have induced a redness of the face as well as of the sexual skin by giving progesterin to an ovariectomized monkey. Mortimer et al.¹⁷ have observed a hyperemia of certain areas of the nasal mucosa concomitant with the activity of the sexual skin. With reference to premenstrual retention of water in the body, Krohn and Zuckerman¹⁵ have demonstrated that swelling of the sexual skin accounts for only a fraction of the total edema, the additional water being distributed in the remainder of the skin as well as in other tissues.

Direct observations have been made of the vessels of living animals after giving estrogen or progesterin. Reynolds et al.¹⁸ found that estrogen dilates the small vessels of the ear of ovariectomized rabbits. Mortimer and his co-workers¹⁷ have observed that giving estrogen causes engorgement of vessels in the nasal mucous membrane of monkeys of both sexes.

Few observations in the human being have been reported and they have been quite limited as regards the areas of skin examined. The effects of estrogen and progesterin on the circulation in the finger have been studied by several workers. Carloni⁶ observed the looped capillaries of the nail fold of normal women. He found that both estrogen and progesterin produced vasodilatation, with an increase in the background coloration of the fold and a diminution in capillary pressure. The effect of estrogen was noted in one-half hour and it lasted for the four hours' duration of the experiment. The dilatation induced by progesterin was intense within two hours but was shorter in its duration. Carloni further found a difference in the site of action of the two hormones. Estrogen, although it caused an enlargement of the entire vascular loop, acted particularly on the arterial limb, so that its size almost equaled that of the venous segment. Progesterin, on the other hand, gave preponderantly a dilatation of the venous half of the capillary loop. Reynolds and his associates¹⁹ studied the effect of estrogen on the nail fold capillaries in women in the menopause. They found a dilatation of the postarteriolar capillaries and venules associated with a diminution in blood flow.

The influence of the menstrual cycle on the state of the nail fold capillaries was also studied by Carloni. He found evidence of vasoconstriction in the early part of the cycle, with vasodilatation in the latter half. His results are somewhat at variance with those of Hagen.¹² Hagen's results, showing vasospasm in the two days preceding menstruation and vasodilatation during menstruation, are open to the criticism that they are based mainly on one cycle in one individual.

Brewer⁵ tested the fragility of the cutaneous capillaries in the antecubital and infraclavicular fossae of women. He found an increased fragility which appeared abruptly on the first day of the cycle and lasted for two or three days. He attributed the fragility to vasospasm.

CUTANEOUS VASCULAR CHANGES IN WOMEN IN REFERENCE TO THE MENSTRUAL CYCLE AND OVARIECTOMY

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THIS report deals with vascular changes in the skin of women in relation to the activity of the ovaries. Two groups of observations are included. The first concerns cyclic variations in cutaneous pigments and blood flow in normal women. The second consists of similar observations in women after ovariectomy. The spontaneous, momentary flushing of the castrate state was not studied. The investigation concerns, rather, more permanent changes in the skin. The effects of estrogen and progesterin upon skin following ovariectomy, were also tested.

Recording spectrophotometry of the intact skin was employed. This technique provides an objective and accurate method of observation which can be utilized over many areas of the body and possesses certain advantage over previous methods. This technique has been used in a similar study of castrated men.⁹

The prototype of cutaneous reaction to ovarian secretion is to be found in the reactions of the "sexual skin" of monkeys. This zone includes the vulva, perineum, buttocks, and contiguous areas. The "sexual skin" is not apparent in males or immature females, but begins to be red and turgid in pubescent females, and maintains this character, with cyclic increase, throughout maturity.^{1, 7} Its relation to ovarian functions is further shown by its regression after ovariectomy. The dermis in this area consists of loose meshed mucoid connective tissue. The vessels are relatively large and numerous and, though the hairs are sparse in this region, the arrector pili muscles are exceptionally developed and show greater reactivity than elsewhere.^{3, 16} The cock's comb is a similar cutaneous area which reacts to gonadal hormones.¹³

Cyclic activity of the sexual skin of monkeys is manifest by redness, swelling, and erection and bristling of the hairs. The swelling is due to an increase in the water content of the mucoid connective tissue, suggesting the premenstrual edema of some women. Activity begins after menstruation, and reaches its height during the third week of the cycle, to subside some time before the onset of the next menstruation.^{1, 3, 7, 15}

The peak of activity has been correlated with ovulation and the discharge of estrogenic hormone by the ovary. The output of estrogen shows two peaks—one in the middle of the cycle and the other just before menstruation. After ovulation the follicle begins to produce progesterin, which reaches its maximum in the last few days of the cycle.²

The influence of estrogen has been shown experimentally by its ability to induce sexual skin activity in ovariectomized and immature female monkeys,

The spectrophotometric determinations were made in a room in which the temperature was maintained at about 70 to 72° F. The relative humidity was kept between 10 and 30 per cent. "The subjects rested for from twenty to forty minutes before readings were begun. Areas of the body habitually uncovered by clothes, such as the hands, were measured last, to allow additional time for the circulation to reach stability. As far as possible, we avoided taking readings at night or soon after meals, since a peripheral vasodilatation may be present at these times.

"A description of the Hardy recording spectrophotometer and a discussion of its use in measurement of the cutaneous pigments have been presented elsewhere.⁸ Briefly, the apparatus records the reflectance of the intact living skin, giving an analysis by wave lengths over the entire visible spectrum, from the violet end at 400 $m\mu$ to the red end at 700 $m\mu$. In the curve thus obtained, each pigment is identified by its characteristic absorption band. The amount of the pigment is indicated by the degree of absorption at the wave length of the band. Lowering of the reflectance at the particular wave length is therefore proportional to the amount of the pigment present. Previous analysis of normal individuals had demonstrated five cutaneous pigments: namely, melanin, a derived material described as melanoid, carotene, reduced hemoglobin and oxyhemoglobin."⁹

Melanin gives marked absorption in the violet end of the curve, since its band lies in the near ultraviolet. Melanoid shows an absorption band at 400 $m\mu$. The bands of carotene are located at 455 and 482 $m\mu$. Ordinarily the band at 455 $m\mu$ is obscured by the absorption of hemoglobin, and only that at 482 $m\mu$ is evident.

The spectral characteristics of oxyhemoglobin and reduced hemoglobin deserve special attention, since these two materials are the ones found to be involved in the skin changes of our subjects. Their absorption bands and the change in the curve with differing concentration are shown in Fig. 1.

Observations

Normal Cyclic Changes.—In normal women fluctuations were found in the two forms of hemoglobin but not in the other skin pigment. In the first week of the cycle, the skin curves showed a small quantity of hemoglobin, with a preponderance of the reduced form. These characteristics of the curve became slightly more pronounced by the time of the mid-cycle (Fig. 2). In our experience, such skin curves represent a sluggish cutaneous blood flow, but without any associated venous dilatation. From mid-cycle on, there was a steady increase in both the quantity of hemoglobin and the proportion of oxyhemoglobin, reaching a maximum in the day or two preceding the onset of menstruation. We construe these changes as indicating a great increase in blood flow in the skin. The change from an active flow at the end of the cycle to a sluggish flow in the beginning of the cycle occurred at about the time of onset of menstruation. More frequent readings than we have made would be necessary to localize the time more exactly.

It is noteworthy that these cyclic variations in blood flow were observed over the entire trunk and at least the upper parts of the limbs. There is suggestive evidence that the face, and the hands and feet, may share in these changes. Yet, for the reasons mentioned earlier, we felt obliged to exclude these zones from our final analysis.

Postovariectomy Changes and Effects of Administration of Estrogen and Progesterin.—Subjects M. H. and E. M. showed essentially the same findings

Material and Methods

Cyclic changes in the skin were studied in five normal young white women. It was assumed that the cycles were ovulatory inasmuch as they were regular, and the menses of moderate duration.²⁰ Further normalcy of the subjects was indicated by the circumstance that each had been pregnant at least once. Only two of the five subjects were studied for more than one cycle. The pertinent data relating to these two subjects are as follows:

SUBJECT	AGE	PREVIOUS PREGNANCIES	DURATION OF CYCLE	CYCLES STUDIED
R. B.	35	1	28 days	3+
M. W.	28	2	32 days	3

Readings were made five to seven days apart.

In addition to the five normal subjects, three ovariectomized white women were studied.* Spectrophotometric readings of the selected areas of skin were made before the administration of the hormones. Estrogen and progestin were administered to the ovariectomized subjects, and readings were taken subsequently at intervals of several weeks. Treatment was then discontinued so that the skin might return to its pretreatment state. Estrogen and progestin were used singly and in combination. A summary of the pertinent data is given in Table I.

TABLE I. SUMMARY OF DOSAGE IN OVARECTOMIZED SUBJECTS

SUBJECT	AGE	TIME AFTER OPERATION	ESTROGEN	TIME OFF TREATMENT	PROGESTIN	COMBINED HORMONES
M. H.	36	2 months	Progynon-B 1 mg. 3 times weekly for 12 weeks	8 weeks	Proluton 5 mg. 3 times weekly for 5 weeks	Proluton 10 mg. Progynon-B 1 mg. Once weekly for 3 weeks
E. M.	38	9 months	Progynon-B 1 mg. 3 times weekly for 12 weeks	9 weeks	Proluton 10 mg. 2 times weekly for 5 weeks	Proluton 10 mg. Progynon-B 1 mg. 2 times weekly for 2 weeks
E. P.	33	One ovary: 5 years. 2nd ovary: 7 months	Progynon-B 1 mg. 3 times weekly for 4 weeks Di-ovocylin 1 mg. 2 times weekly for 4 weeks	8 weeks	Proluton 5 mg. 3 times weekly for 5 weeks	Proluton 5 mg. Di-ovocylin 5 mg. 3 times weekly for 2 weeks

Progynon-B: Alpha-estradiol-benzoate, in oil. Schering.

Di-ovocylin: Alpha-estradiol-dipropionate, in oil. Ciba.

Proluton: Progesterone, in oil. Schering.

All administration was intramuscular.

In both normal and ovariectomized groups, readings were taken of areas of the skin of the trunk, as well as on the upper and lower limbs. The face, hands, and feet were found to be unsuitable, since they are subject to change through exposure to sunlight and other influences, including unusual lability of the circulation. Because of these factors, we were unable to obtain basal conditions in these latter areas. This was unfortunate since there is evidence that face, hands, and feet may be influenced by sex hormones. At any rate, we can say with certainty that if changes did occur in the hands and feet they were not of the magnitude we had observed in the case of male castrates.

*Referred from the Free Hospital for Women, through the courtesy of Dr. John Rock.

The effect of the administration of estrogen was to increase the amount of hemoglobin present and to accentuate the twin absorption bands of oxyhemoglobin (Fig. 3). We interpret these findings to indicate an increase in cutaneous blood flow. A single large dose given to subject, M. H., when she was off treatment elicited the effect within four hours.

When the subjects were taken off estrogen, the curves reverted to their pre-treatment levels. However, upon the administration of progestin, oxyhemoglobin increased again. The effect of progestin was somewhat more marked than that of estrogen in heightening the ratio of oxyhemoglobin to reduced hemoglobin. The total amount of hemoglobin varied and was often diminished by the treatment. It should be noted that neither hormone gave as much increase in blood flow as had been seen in male castrates after testosterone.

The combined use of estrogen and progestin was not long tolerated by the subjects, mainly because of the advent of pain in the breasts. After combined administration, the curves showed a striking lack of hemoglobin and an increase in the proportion of the reduced form. We interpret this as evidence of a sluggish blood flow.

Discussion

Our observations show that ovariectomy does not entirely change the basic peculiarities which distinguish the female from the male skin. Similarly, the male castrates previously studied had maintained to some extent, their differences from the female. In both sexes, therefore, we can assert that sex differences are basically due to genic influence. This base line of pigmentary characteristics is then modified by the presence of the sex hormones. Unlike the situation in many other animals, where reactivity to the hormones is localized in special areas, the human skin reacts probably in its entirety.

In the male castrates, where the greatest changes were in hemoglobin as related to cutaneous blood flow, there were, in addition, some variations in the other skin pigments as well. A striking reduction was found in the total amount of hemoglobin with a relative increase in the proportion of the reduced form. In areas with a large venous bed, a real increase in reduced hemoglobin was observed, suggesting venous dilatation. A slight diminution in melanin formation occurred with an increase in the derived pigment melanoid. Finally, carotene storage increased in the entire integument. All of these changes could be reversed by the administration of testosterone propionate. In females, ovariectomy induced a reduction and sluggishness of blood flow but the more static pigments were not affected. Moreover, no evidence of venous dilatation was noted in areas with normally extensive venous networks, such as was seen in the men.

The part played by estrogen and progestin in the correction of the ovariectomized state has been demonstrated. Each given singly increased the cutaneous blood flow. Estrogen gave a volume increase as well, which progestin did only inconsistently. Our findings are in general agreement with the evidence of former workers that these materials produce vasodilatation. It is known that the entire blood volume of the ovariectomized patient is diminished but will increase again on the giving of estrogen.¹¹ That this alone could be responsible for the increase in cutaneous blood volume seems unlikely in view of the rapidity with which the administration of estrogen alters the skin curve.

through their respective courses of observation. Subject E. P., who had had one ovary removed five years, and the second seven months, before the study, showed inconsistent results, suggesting the presence of a remnant of ovarian tissue, or of some extragenital source of material supplanting the ovarian hormones.

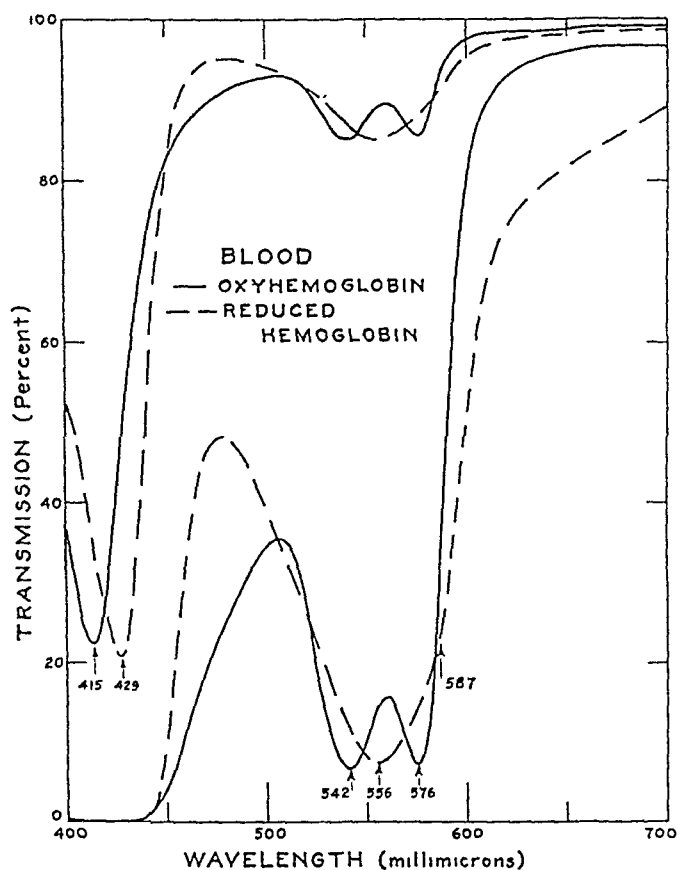


Fig. 1.—The transmission of reduced and oxyhemoglobin. In the lower curve the blood was diluted 1 to 100; in the upper curve it was diluted 1 to 1,600. Oxyhemoglobin shows a pair of absorption bands at 542 and 576 $m\mu$. In reduced hemoglobin these bands are replaced by a single band at 556 $m\mu$. The general shape of the curves is also useful in determining the relative quantities of these two materials.

Ovariectomy did not remove those pigmentary characteristics which distinguish the female from the male. As previously reported,⁸ these are as follows: The female skin shows less melanin and less hemoglobin than the male. Areas primarily rich in melanin show a comparatively higher melanin ratio over poorly pigmented areas than is the case in the male. The buttocks are predominantly arterial (high in oxyhemoglobin) in the female, while they are predominantly venous (high in reduced hemoglobin) in the male. There is more carotene in the female breast, abdomen, and buttocks than in the corresponding regions in the male.

Only one variation from the normal occurred in the female castrate—a diminution in the total amount of hemoglobin, with a slightly increased proportion of reduced hemoglobin over oxyhemoglobin. These findings probably represent a diminution in the cutaneous blood flow.

We had found similar changes in male castrates, but it was apparent that the change in females was somewhat less marked in degree. Moreover, there was no clear evidence of venous dilatation in the more "venous" areas of the body, such as had been observed in the male subjects.

There is sufficient tide in the levels of estrogen and progestin in the intact woman to account for the appearance of the skin in the first half of the cycle. At this time there is neither much estrogen nor progestin in the body (Fig. 4). As the follicle ripens, estrogen is formed but does not reach high levels until late in the cycle. It is at this time that the skin curve indicates a more active blood flow. The two additional features of the activated sex skin of the monkey, edema and pilomotor activity, may also be represented in the human being. Premenstrual edema of women is a well-recognized entity, but, to our knowledge, increased pilomotor activity has not been reported. However, personal clinical observation enables us to assert that increased pilomotor response can be demonstrated in women at about mid-cycle.

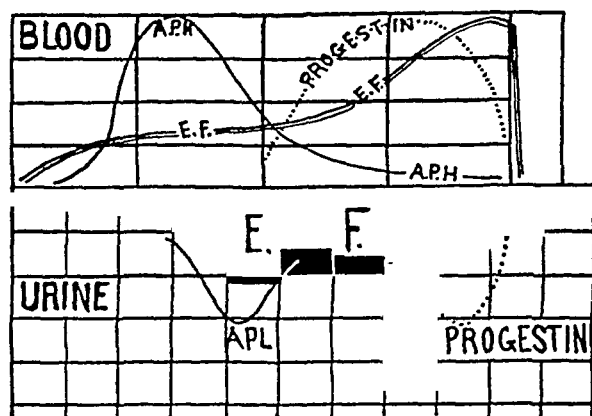


Fig. 4.—Current concepts of the cyclic tide of the female sex hormones, from Frank.¹⁰ E. F., estrogenic factor. A. P. H., anterior pituitary gonadotropic hormone. A. P. L., anterior pituitary-like gonadotropic hormone.

The progestin curve of the blood is theoretical, by deduction from measurements of pregnandiol excretion in the urine.

Progestin becomes appreciable in the latter half of the cycle. We have seen that the simultaneous administration of the two hormones diminishes the amount of cutaneous blood and its activity so that it resembles that of the castrate state. It would seem paradoxical that the curves of normal women continue to show an increasingly active flow in the latter few days of the normal cycle. This paradox is resolved if we recall the observation of previous workers that the modification by progestin, of estrogen influence on the sex skin of monkeys, requires several days. Presumably in normal women modification occurs about the time of menstruation. We cannot rule out the possibility, however, that the differing conditions of ovariectomized and normal women may cause a variation in the effect of the combined hormones.

Summary

The skin of trunk and limbs of three ovariectomized and five normal young women was studied with the Hardy recording spectrophotometer. In both groups of subjects the pigments of the skin were unchanged excepting reduced

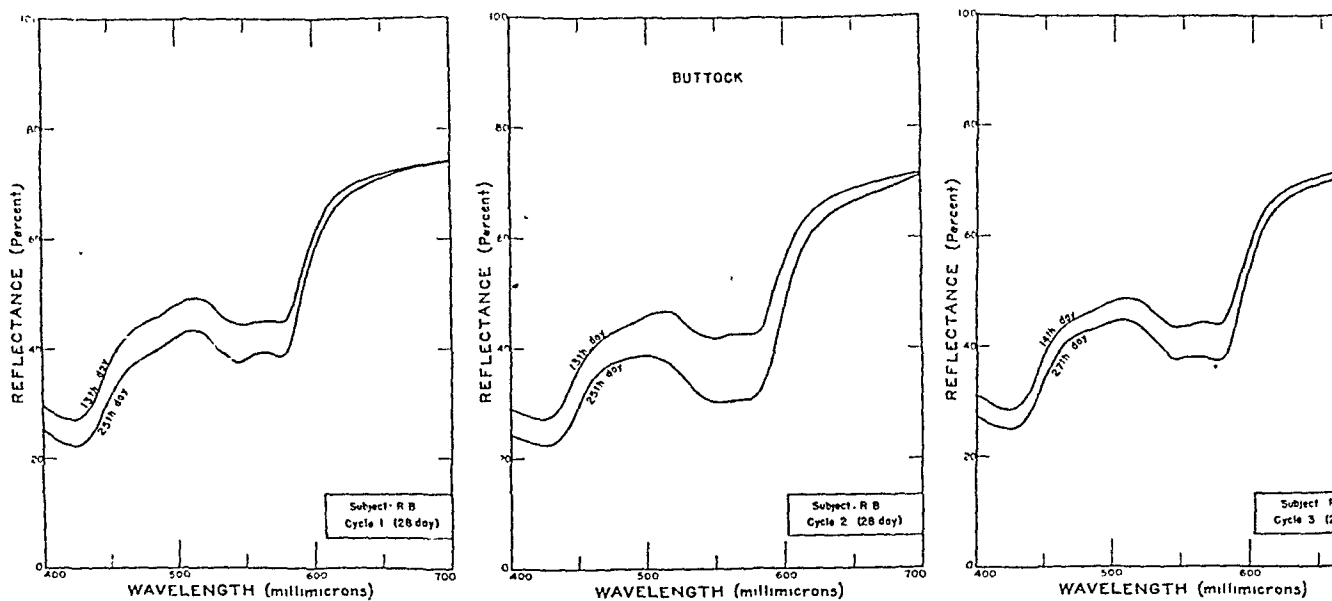


Fig. 2.—Normal cyclic change in the spectrophotometric curves of the buttocks during three successive cycles. In each cycle the earlier curve shows little hemoglobin, which is rather poorly oxidized. The later curve shows an increase in hemoglobin, with dominance of the oxidized form.

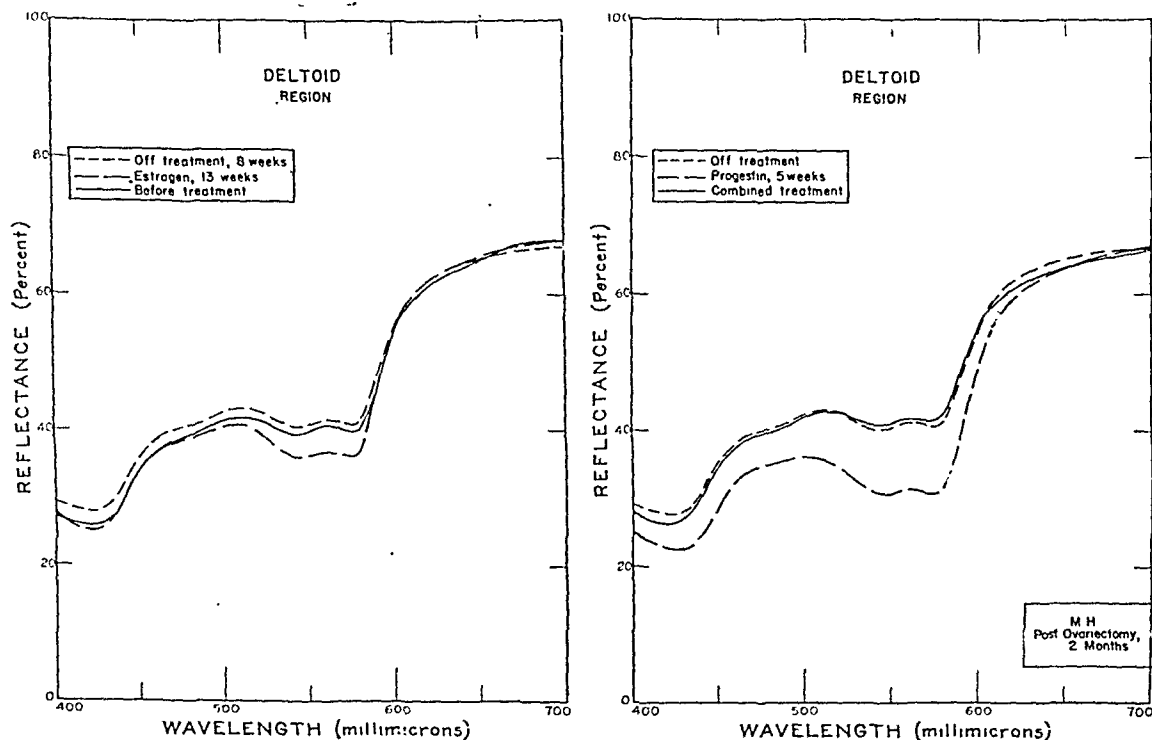


Fig. 3.—Spectrophotometric curves of the deltoid region of an ovariectomized subject. On the left, the pretreatment curve is low in hemoglobin content, and with dominance of the reduced form. After treatment with estrogen, the curve shows a real increase in oxyhemoglobin. With cessation of treatment, the curve reverts to its pretreatment character.

On the right the administration of progestin produces a marked increase in oxyhemoglobin. The combined use of progestin and estrogen diminishes the hemoglobin content causing the curve again to revert to its off-treatment level.

CHANGING CONCEPTS OF X-RAY PELVIMETRY*

A. E. COLCHER, M.D., AND WALTER SUSSMAN, M.D., PHILADELPHIA, PA.

THE use of x-ray has given impetus to the study of pelvimetry and the female pelvis, resulting in the development of many techniques. We desire to review the changing concepts of x-ray mensuration, discuss its related problems, and suggest a solution.

X-Ray Measuring Devices (Fig. 1)

The Thoms¹³ technique uses a very large appliance with a perforated centimeter grid for measuring chiefly the inlet. The patient must be removed from the table for the second lateral exposure.

Javert and Steele⁷ developed a modification of the Thoms, combining a notched centimeter ruler with a distorted scale as a final measuring device, and used the precision stereoscopic method developed by Caldwell, Moloy, and Swenson.² This latter technique, elaborated by Swenson with stereoscopic and lateral films, constitutes a very complete study.

The Ball¹ calculator is an empirical volumetric examination with construction of a sphere from the diameters.

The Snow-Lewis¹¹ Slide Ruler by geometric formula can solve the original object diameter. Many calculations are necessary.

In the method developed by the authors,³ a rotating ruler with centimeter perforations is placed beside the body in both the anteroposterior and lateral positions taken at approximate right angles to each other at any distance. Direct readings are made on each film.

Any of these devices and many others long in use by the radiologist should give accurate results. Therefore, accuracy in pelvimetry is not a problem.

Diameters of the Pelvis

No attempt will be made to discuss in detail all the suggested diameters of the pelvis (Fig. 2). There are many of them from the inner sacrum to the inner symphysis. Of the true pelvis alone, there are at least twenty suggested diameters, but only the more recent concepts will be discussed.

The coccyx may be eliminated as a criterion for measuring diameters. Newer concepts indicate that it is not as important as it seems, because it is a mobile unit and presents no real obstacle, unless it is fixed or abnormally large and forward.

The true conjugate diameter has no corresponding transverse diameter, and is well above the brim of the true pelvis. The literature tends to show that the so-called conjugata vera is not a critical factor in the progress of labor. Since the conjugata vera is in the false pelvis, it could be named more properly the "false conjugate."

Let us evaluate the diameters of the true pelvis. The drawings in Fig. 1 show some of the various diameters of the pelvis. Thoms,¹³ Javert and Steele,⁷ and Ball¹ do not indicate any particular relationship between their anteroposterior and transverse diameters.

Snow and Lewis¹¹ form a three-level pattern with their transverse diameters. The inlet is formed by its greatest transverse diameter, the midpelvis between the spines of the ischium, and the outlet between the tuberosities of the ischium. These diameters are also used by the authors.

*Presented at a meeting of the Philadelphia Obstetrical Society, Jan. 8, 1948.

hemoglobin and oxyhemoglobin. Results in the hands and feet were inconclusive, and the face was not studied.

After ovariectomy, the sexual characteristics of the female skin do not disappear, suggesting a genic control. A diminution in vascularity is noted, evidenced by lowering of the amount of hemoglobin with a relative preponderance of the reduced form. Administration of estrogen was followed by an increased cutaneous blood flow with an actual increase in oxyhemoglobin. Progesterin markedly increased the proportion of oxyhemoglobin, but did not consistently increase the total hemoglobin. The combined administration of both hormones results in a diminution in hemoglobin with a predominance of the reduced form.

In the early part of the normal cycle, the curves resemble those obtained from ovariectomized subjects. After mid-cycle, there is evidence of greatly increased vascularity which reaches a maximum in the premenstrual period. This is consistent with the observed effects of the two hormones acting in the latter half of the cycle, since previous workers have shown that progesterin takes several days to modify estrogen effect.

Unlike the situation in many other mammals, in which reactivity to the female sex hormones is localized in special areas, the human skin probably reacts in its entirety.

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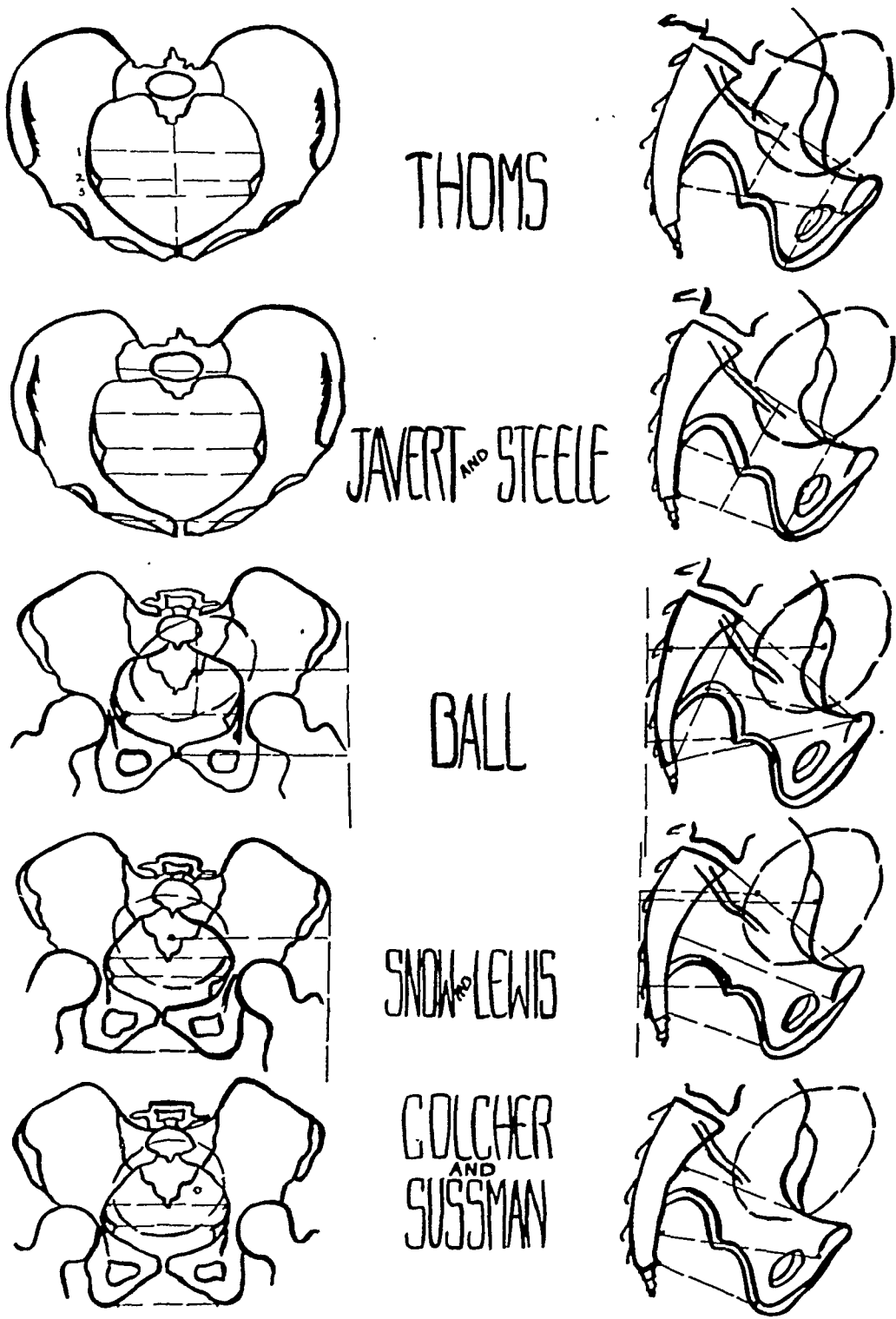


Fig. 2.—Pelvic diameters.

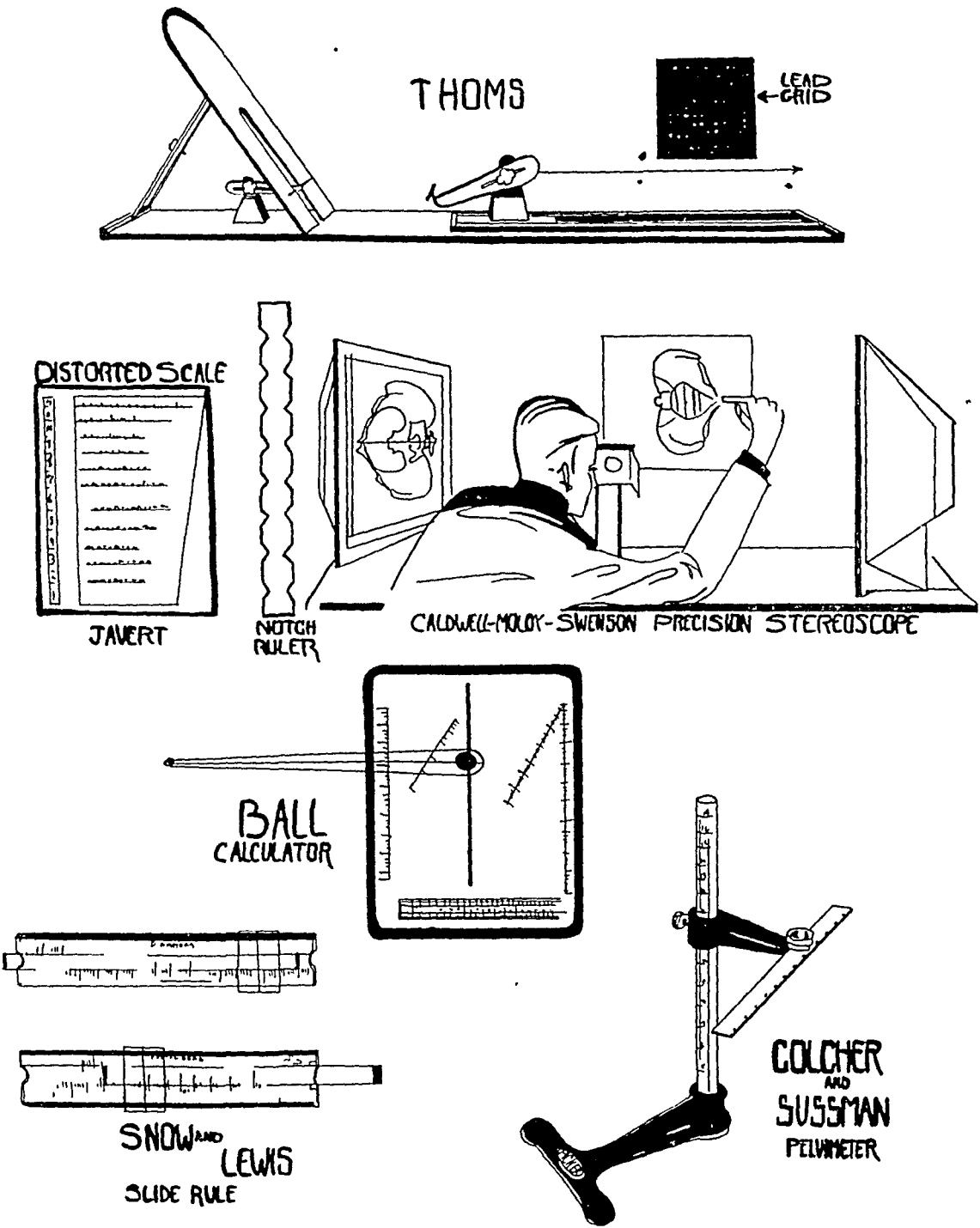


Fig. 1.—X-ray pelvimetry devices.

Concerning the anteroposterior diameters, Ball¹ and Lewis¹¹ continue to use the conjugata vera, whereas Thoms¹³ and Javert and Steele⁷ have now discarded the conjugata vera and move down toward the true pelvis for the obstetric conjugate. This conjugate is at the brim of the pelvis. The authors move into the true pelvis and utilize the level of the transverse diameter of the inlet which on the film is located about midway between the brim of the pelvis and the sacrosciatic notch. A line is drawn from the upper symphysis through the inlet diameter and extended to the sacrum, completing the diameters of the inlet. These intersecting diameters, previously described by the authors (Fig. 3),⁴ may now form a plane completing the first bony ring of the true pelvis through which the fetal head must pass. The actual inlet can thus be divided into anterior and posterior segments.

To continue this pattern, the midpelvic plane is drawn from the lower symphysis through the middle of the transverse ischial diameter and extended to the sacrum. This also forms a plane and creates both anterior and posterior segments. The outlet plane, between the tuberosities of the ischium and the tip of the sacrum, now forms the posterior segment or triangle of the outlet. This triangle has additional space forward under the subpubic arch. With this technique, all the salient bony factors of the true pelvis are utilized. Any one segment can be individually measured directly from the film.

Positioning of the Patient for Pelvimetry

Concerning the position of the patient for the anteroposterior diameters (Fig. 3),³ the lateral view has definitely been standardized. The patient lies on her side, and the ruler, with centimeter markings, is placed at the midsacrum. The distortion of the diameters is the same as that shown by the ruler, and direct readings can be made. This method justly enjoys popular usage and is invaluable in x-ray pelvimetry. Erect films may also be made in like manner.

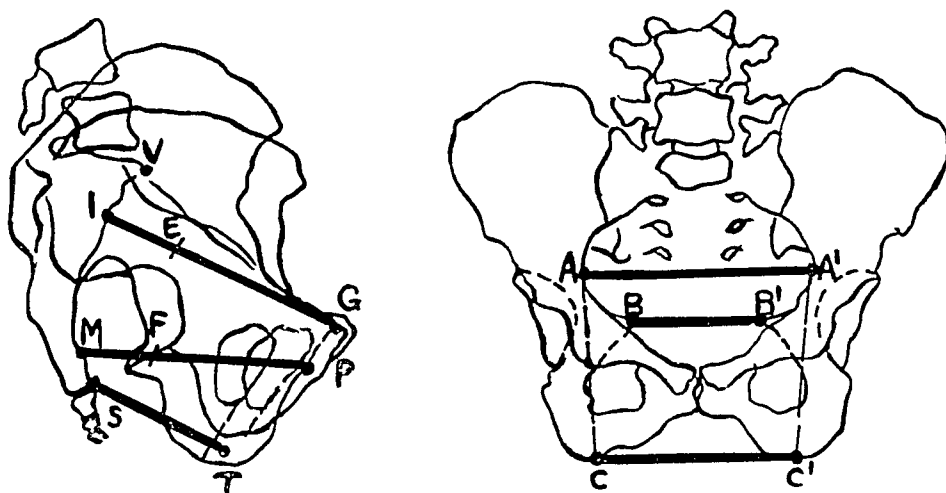
In positioning for the transverse diameters (Fig. 5), Thoms¹⁴ has the patient reclining at an angle on a special apparatus. This position elevates the sacrum, lowers the forepelvis, and allows direct visualization of the contour of the inlet. With the patient recumbent and with various-sized pads placed under the back, Javert and Steele,⁷ Snow and Lewis,¹¹ and Ball¹ show a gradual lowering of the back with a gradual elevation of the forepelvis. In our technique (Fig. 4b),³ the knees are flexed, the spine is flat, and greatest elevation of the forepelvis is attained; the midpoints of the inlet, the spines of the ischium (midpelvis), and the tuberosities of the ischium (outlet) are on the same plane in relation to the tabletop and, thus, on the same level with the film placed in the x-ray table. By placing a centimeter ruler at the level of the tuberosity of the ischium, all the transverse diameters are measured directly on the film with the same distortion as that on the ruler. *The very same technical factors for measuring the pelvis in the lateral view are now possible in our anteroposterior positioning.*

When the head is the presenting part, the fetal head diameters are also measured with the same ruler. While the over-all measurements of the fetal head should be considered, we believe that the suboccipito-bregmatic and biparietal diameters are of greater importance. A table gives the subpubic angle in degrees.

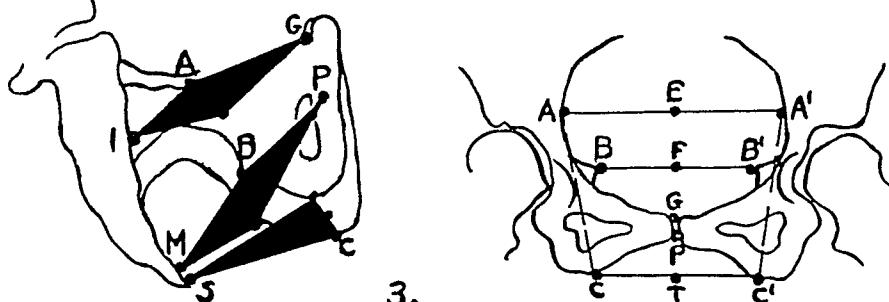
Practical X-ray Evaluations

The number of x-ray pelvimetric methods published emphasizes and justifies its use in obstetrics. We believe that it has definitely been shown that the external measurements and maneuvers of a physical examination are not only

1.
INTERSECTING DIAMETERS OF PELVIS



2.
PLANES OF PELVIS



3.
TRIANGLES OF PELVIS

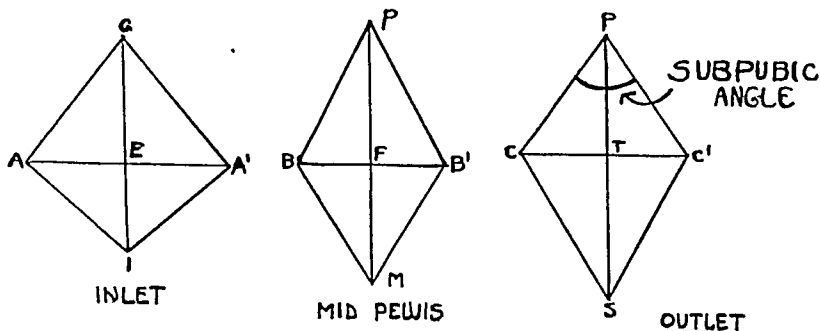


FIG. 3.—1. Intersecting diameters of the inlet, midpelvis and outlet.
2. Perspective view of the three planes of the true pelvis, including the intersecting diameters. The subpubic angle is C-P-C'.
3. The triangles of the pelvis with both the anterior and posterior segments may be reproduced in life size with the same films.

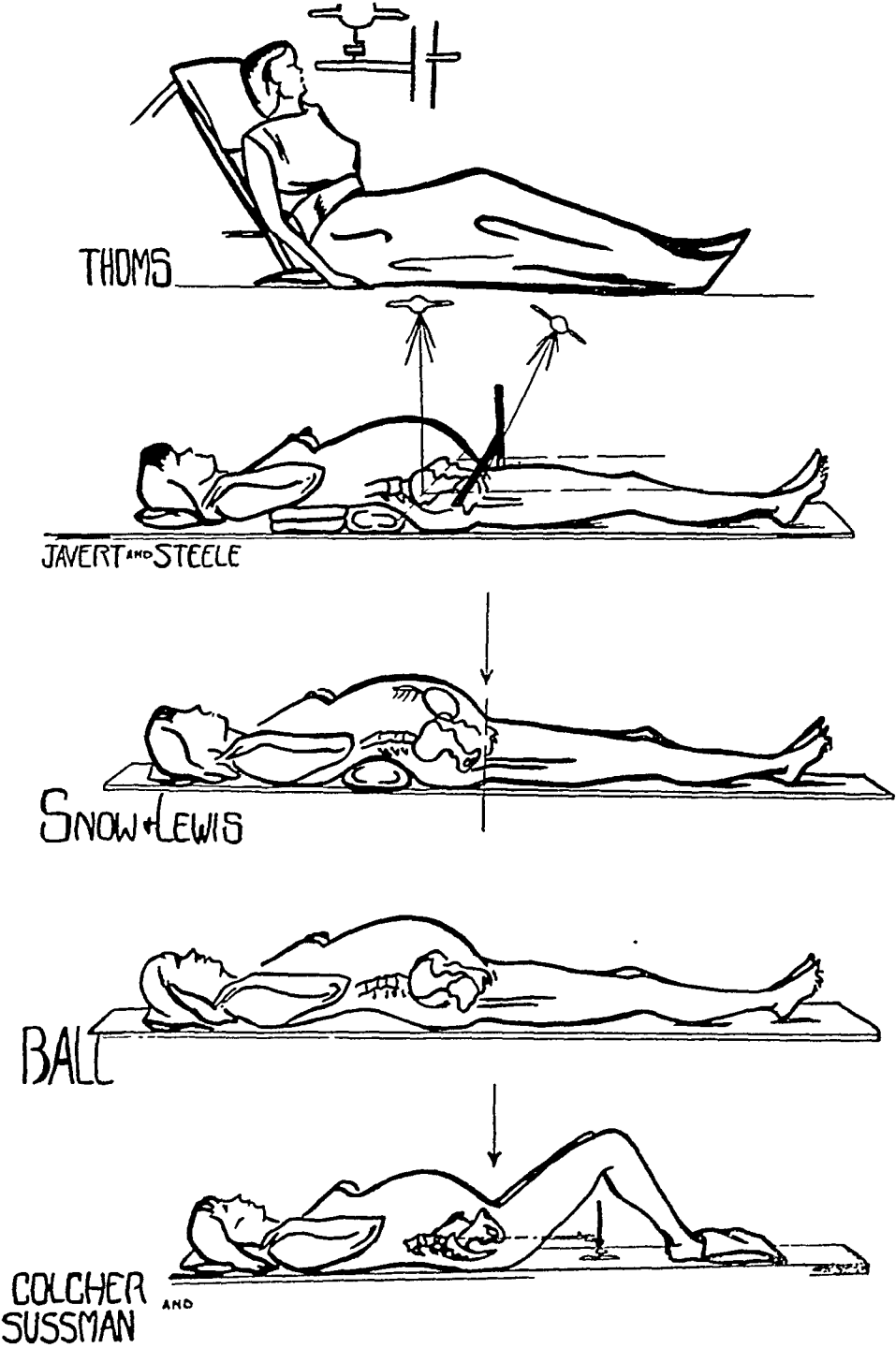


Fig. 5.—Various positions for anteroposterior films

unsatisfactory but questionable as to accuracy. For instance, J. T. Williams,¹⁵ after examining externally 300 primiparas, found that many with broad hips and large external measurements had contracted outlets and narrowed subpubic angles, while many of those with narrow hips had broad outlets with ample transverse diameters of the outlet and wide subpubic angles. Jareho⁶ states that most estimates of the size of the pelvic inlet, when done by physical examination, are inexact and unreliable. Thoms¹⁴ says that the most careful external measurements are unreliable. According to Rohan Williams,¹⁶ the possible disproportion between the head and the pelvis is one of the most difficult things to determine in obstetrics, and he concludes that clinical measurement of the true conjugate is either impossible or inaccurate, except in cases of severe pelvic contraction. By the same token, these men indicate that only by proper x-ray pelvimetry can an accurate determination of the necessary factors of the pelvis and fetal head be made possible.

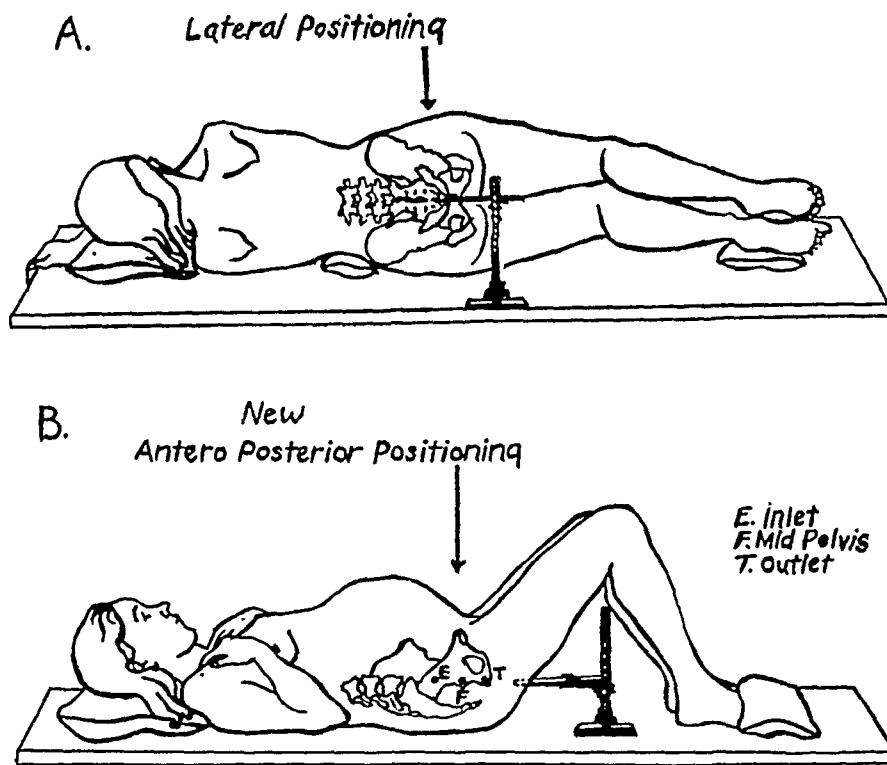


Fig. 4.—A. X-ray position for the lateral view with the centimeter ruler at the mid-sacrum.

B. New positioning for the anteroposterior film with the centimeter ruler at the level of the tuberosity of the sacrum (T). Midpelvis at spines of ischium (F), and inlet at (E) are all on the same level.

Stander,¹² in his recent book, says, "I believe the reduction in fetal mortality from 3.6 per cent in 1932 to 2.2 per cent in 1943 is in part due to the integration between clinical and x-ray pelvimetries." Thoms¹⁴ x-rayed 1,100 primiparas with only 2.3 per cent cesarean sections.

For many years, one of us (Sussman) has been educating his patients for x-ray pelvimetry. Various techniques were used until the evolution of our technique with a series of 450 cases since 1943. These included routine studies of all primiparas and multiparas with previous history of difficult labors. The films were taken about ten days before term. The most troublesome question

Discussion

DR. PAUL C. SWENSON.—During the past five years I have combined the method of pelvic measurement by these authors with stereoscopic films and have been able to obtain equally good studies of the female pelvis as I did with the precision stereoscopic means alone. In fact, the method has proved to be easier and less expensive as well.

Drs. Colcher and Sussman should be congratulated on having called our attention to the necessity for unanimity of thought, if not technique, as far as x-ray methods are concerned in obstetrics. It is obvious that the mere mensuration and typing is not the important thing. We must have a standardization of thought as well as a means of mensuration. The actual measurements are not the important thing. Any method well done can be developed to a sufficiently accurate stage in anyone's hands, but the proper approach, interpretation, and correlation of clinical findings are important.

The essayists would like to have some sort of standard terminology applied to mensuration. This is commendable. We have several indices of size and disproportion which seem to work out well in any one individual's hands, but not in others. The difficulty is that no hard and fast rule can ever be made. I have seen exceptions to all rules and therein lies the danger of certain hard and fast indices. The over-all picture must always be kept in mind.

At the present time, our chief difficulty has been in trying to measure the fetal head accurately in order to estimate the fetal weight. I have not been able to be certain of this procedure at all, no matter how accurate I try to be using the methods of Snow and Ball. I find that there are just too many variables. This is in agreement with the findings of others. Donaldson of Ann Arbor, for example, has recently checked several methods in a large number of cases and finds that he can be accurate within one-half pound in only one-third of the cases. To those, therefore, who look for the last word in these methods of mensuration, I give only a word of warning that they are fooling themselves since too much reliance is placed on these procedures alone. They are important, but not the whole story.

I always like to think of the words of DeLee who, after warning of all the pitfalls in pelvimetry alone, immediately follows this by the remark that he would, nevertheless, not be without pelvimetry, but the findings should always be taken in conjunction with the clinical situation.

With regard to the level of the true conjugate, it was Caldwell's considered opinion that because, in the usual case, the symphysis was below the level of the promontory and therefore in a different plane, the diameter past which the fetal head had to pass when engaged by both the anterior and posterior bony limits was definitely lower than it was usually thought to be. It usually falls along the iliopectineal line. This particular point was determined by following cases through labor with films at varying intervals, thereby watching the adaptation of the fetal head to the inlet.

I did not mean to imply in my first discussion that there was any difficulty in interpreting the diameters as we measure them, but rather that when we have these various diameters measured it becomes difficult to make anything out of the data at all, if one does not individualize each case and discuss it with the obstetrician, for a correlation with the known clinical background. If one does not do this, one might just as well discard the x-ray evidence. I think we are all agreed that in many cases pelviography is a very important adjunct, but I think it can be stated without argument that the negative evidence is perhaps the most important; that is to say, if a well-formed, roomy, and adequate pelvis is found with an average-sized fetus, there is one cause for dystocia which can be eliminated; namely, bony obstruction. Therein lies 90 per cent of the value of the examination. When, however, there is borderline disproportion, the measurements become of less importance. The clinical background, the fetal pelvic relationships, and the pelvic type then are of greater importance in the management of the individual case.

DR. A. E. SCHUMANN.—I have on many occasions enjoyed watching the stereoscopic progress of labor as demonstrated by Dr. Caldwell and was delighted and amazed by the

was the use of emergency x-ray outside of technical working hours. Cumbersome technique and difficulty in reading the films were also obstacles. With our present method, the obstetrician can easily learn to read his own films and correlate this with his clinical art. Our cesarean section rate (uncorrected) from 1943 to, and including, 1946 was 6 per cent, and in 1947, 3.7 per cent. We had five patients delivered per vagina who had had previous cesarean sections. No babies were lost due to cephalopelvic disproportion.

Conclusions

While our series of 450 cases is not large, our statistics, as well as the cases mentioned, tend to show a decrease in the incidence of cesarean section in cephalopelvic disproportion and a decrease in fetal mortality. And yet the radiologist seems to avoid this type of examination. Why, with all its advantages, is x-ray pelvimetry not more popular? The reason, we believe, is self-evident. Despite the driving interest in this type of investigation—from Granzow,⁵ who first introduced a measuring ruler, to the present time (about 422 articles on pelvimetry in the last 18 years)—and the innumerable measuring improvements devised, the x-ray reports and interpretations remain confusing. An obstetrician who has several hospital connections may find that each hospital will use a different technique, different diameters, and different elements of evaluation. As a result, the practical values are obscured.

No universal language or technique is at present employed wherein radiologists and obstetricians may use the same terms and make like interpretations. A similar situation was recognized almost half a century ago when the American Gynecological Society, in 1905, appointed a committee, Drs. King, Williams, and Davis,⁸ for this purpose, and a series of compromise diameters and measurements was published and accepted. There were thirteen diameters at that time. Today there are many more, with one author stressing his own concept of the proper diameters, and another stressing his apparatus and technique, all of which results in confusion.

It would, therefore, seem timely to consider means of formulating standards for a universal technique and terminology.

We have made an effort to describe the changing concepts in x-ray pelvimetry, and suggest that one of the techniques should be accepted and that it should be simple and concise enough to be accurate in the hands of both the radiologist and obstetrician.

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EXTRAPERITONEAL CESAREAN SECTION IN THE PROFOUNDLY INFECTED PATIENT*

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ONE of the advances in modern obstetrics has been the simplification and clarification of techniques for extraperitoneal cesarean section. Though Sellheim, Frank, Latzko and others might be mentioned as leading figures in the development of this operative approach, Waters^{1, 2} and Norton³ have added to the recent refinement of this type of cesarean section and, in their large series of cases, have shown this approach to be practical, safe, and within the technical skill of the trained obstetric surgeon.

However, as sometimes is seen during the development of a new approach to a problem of long standing, this technique has not everywhere met with praise. In fact in some quarters its use is severely denounced. It would seem that there has risen a difference of opinion over the general efficacy of and indications for this procedure which threatens to develop into a controversy as bitter as that of a few years ago between classical and low cervical cesarean section.

It has been estimated in recent years that at least 38 per cent of all cesarean section deaths are due to infection.⁴ The majority of these are due to peritonitis⁵ and follow operations of the transperitoneal type. These usually have been done upon patients who have had long labors, with ruptured membranes for a considerable period, or upon whom there have been frequent vaginal examinations or attempts at delivery. It is, therefore, quite evident that we are, at the present time, faced with the problem of improving this regrettable situation. We may hope that methods which will more positively diagnose the state of the pelvis, the pliability of the soft parts, and the more exact potentialities of the uterine musculature to contract normally and vigorously may be developed in the future to help prevent such things from happening. In the meantime, however, while we are working toward this end, the stark reality remains that we are occasionally bound to be confronted with such badly infected cases.

The fact that each succeeding hour of labor, ruptured membranes, or a combination of the two increases the probability of intrauterine infection has caused modern clinics to attempt to manage cases with this in mind. Certain rules are set up which preclude further procrastination after a certain interval and often dictate the procedure allowed for delivery after a predestined deadline of time has been reached. An excellent example of such a set of standards is that followed by Dieckmann⁶ at the Chicago Lying-in Hospital. He lists the following as contraindications to transperitoneal cesarean section:

*Read at a meeting of the Philadelphia Obstetrical Society on Jan. 8, 1918.

ability to demonstrate the mechanism of labor. I am forced to the conclusion that x-ray pelvimetry is quite difficult. I would even venture to disagree with Swenson. I do not think this subject too important. Though the authors do not seem to think the promontory is of any importance, I seem to remember cases of many fetal heads that failed to get beyond that level. Obstetricians should make the textbook of Ilugh L. Hodge, in which the pelvic planes are described, required reading. I do know that by the Thoms technique it is perfectly possible to measure the size of the pelvic inlet laterally and posteriorly within 2 mm. of the actual measurement. We did an interesting experiment in Kensington Hospital some years ago. Two hundred gynecologic cases were subjected to a special study and when the patient went to the operating room accurate measurements were made and recorded on the operation sheet. When the patient was convalescing from the operation, she was x-rayed by the Thoms technique. She was then subjected to external pelvic measuring and that was recorded on a separate sheet and we then reviewed her obstetric history, if any. When these factors were all assembled as to patients, we found that the obstetric history as related to pelvic measurements, whether x-ray or other method, was singularly variable. Women who we thought would have difficulty delivered spontaneously and the capacious pelvis frequently had required cesarean section. We found external pelvimetry bore no relation to the actual size of the pelvis. In particular, the most disappointing was the diameter of Baudelocque. We did find in all our cases the measurement by the technique of Thoms when compared with the actual measurement in the open abdomen was accurate to within 2 mm. To me, if I am given the size of the pelvic inlet and its shape, I am not much concerned about any other measurement of the pelvis unless it is curiously deformed. Given the size and shape of the inlet and the other factors of the quality of uterine contractions, size of head, and presentation of the head, I think it is only pelvic diameter that is required and that only that is of any service. The Ball technique has been a notable failure in my experience.

DR. SUSSMAN (Closing).—In the literature the term cephalopelvic disproportion is defined as dystocia, including bony and soft tissues. In this paper we define it sharply as a true disproportion between the bony presenting part and the actual bony pelvic structures.

Dr. Swenson states that about 2 per cent of obstetric cases fall within the disproportion group. Dr. Thaddeus Montgomery, in a cesarean survey, found that about 42 per cent were done for cephalopelvic disproportion. More recently, Andrews, Nicholls, and Andrews found their statistics showed almost 50 per cent.

We know that x-ray films do not permit guessing. All available facts are in the obstetrician's hands. The obstetrician should go over the films and correlate the findings with his clinical observations. In our series of approximately 450 cases, we have cut our cesarean rate to 25 per cent. We have lost no mothers or babies due to true cephalopelvic bony disproportion.

We suggest that the obstetrician should know all the facts. We plead for a universal nomenclature. We know that the maternal and fetal morbidity and mortality will be astonishingly low if you take care of the complicated 2 per cent of cases. Only by routine x-ray pelvimetry can you save life and avoid disability.

DR. COLCHER (Closing).—Dr. Montgomery brings up an important issue concerning the value of the true conjugate and obstetric conjugate versus the authors' actual inlet. We have shown, on dried specimens of the pelvis of the young female, that the actual inlet is the first complete bony ring through which the fetal head must pass before a delivery is possible. This inlet is usually well below the promontory of the sacrum, and lies on a level with the greater transverse diameter of the inlet. Thus, a fetal head may pass through a narrow true conjugate, like a rubber ball passing between two points, but will encounter great difficulty in passing through a constricted circle of bone. That is the basis for the new location of the actual inlet.

Dr. Schumann believes the inlet is important, and Dr. Montgomery indicates the inlet and outlet as important. We believe the obstetrician should be fully informed on all measurements and diameters, and utilize what he deems important in that particular instance.

Finally, to obtain good results, there must be cooperation between the radiologist and obstetrician. Otherwise, the value of pelvimetry becomes questionable.

within 1 cm. of the ischial spines. The cervix was half effaced and 4 cm. dilated. The clinical measurements of the pelvis were small but upon x-ray done earlier there was no report of disproportion.

Penicillin and sulfadiazine had been started a few hours earlier. An extraperitoneal cesarean section was performed under continuous spinal anesthesia. The uterus was filled with foul-smelling pus and its wall was gray and necrotic for a depth of about one-fourth inch. The child, a 7 pound, $2\frac{1}{4}$ ounce boy, was living and recovered uneventfully, although it carried with it a foul odor for several days and was given penicillin. The patient was quite ill for three days postoperatively but developed no sign of peritonitis. There was a low-grade fever for twelve days and the incision drained for eight days. The highest temperature after operation was 102.8° F. She was discharged in good condition on the 20th postoperative day.

CASE 2.—(Philadelphia General Hospital.) A 36-year-old Negro, para 0, gravida ii, at term, was first seen after over 60 hours of labor and 53 hours of ruptured membranes. She appeared to be at the point of death with a fever of 103.4° F. and a poor pulse of 170. She was toxic and psychotic, respirations were irregular, and there were many râles at the lung bases. The uterus was very tense and tender, although there were still irregular uterine contractions. No fetal heart sounds were heard. Examination revealed a vertex presentation in right occipitoposterior position at minus one station. The cervix was partially effaced and 3 cm. dilated. Clinical measurements showed outlet to be contracted. Penicillin had been given for twenty-four hours before the patient suddenly became critically ill. After some supportive preoperative care, an extraperitoneal section was done under local anesthesia and a 7 pound, 15 ounce stillborn boy delivered. The uterus contained a large amount of foul-smelling pus which was under such pressure that it spurted several feet when incised. The uterine lining was gray and necrotic. Cultures revealed *Streptococcus hemolyticus*, *Staphylococcus aureus*, and *Bacillus coli*. The patient's condition improved from the moment the uterus was evacuated. The highest temperature postoperatively was 103.4° F., although there was a low-grade fever for fifteen days and drainage from the wound for sixteen days. A transient mild thrombophlebitis responded to conservative therapy. She was discharged in good condition on eighteenth postoperative day.

CASE 3.—(Philadelphia General Hospital.) A 30-year-old Negro, gravida i, para 0, at term, was first seen after 168 hours of labor and 240 hours of ruptured membranes. She had a borderline pelvis and secondary uterine inertia. Her temperature was 102.4° F. This had been preceded by a chill and a temperature of 106° F. Adequate doses of sulfadiazine had been given for over 48 hours and penicillin for 24 hours before the patient became critically ill from infection. The pulse was 130. The uterus was tense and tender and there was a foul vaginal discharge. Examination revealed the vertex molded to within 1 cm. of the spines. The cervix was 3 cm. dilated and partially effaced. An extraperitoneal section was done under continuous spinal anesthesia and an 8 pound stillborn infant delivered from the pus-filled necrosis-lined uterus. The highest temperature postoperatively was 102.4° F., but there was a low-grade fever for ten days. The wound drained for eight days. She was discharged in good condition on the sixteenth postoperative day.

CASE 4.—(Episcopal Hospital.) A 24-year-old, white, gravida i, para 0, at term, was seen after 100 hours of labor and 60 hours of ruptured membranes. The patient was weak and acutely ill with a temperature of 101.4° F. and pulse of 124. There was mild tenderness of the uterus and a foul vaginal discharge. Examination revealed cephalopelvic disproportion and the head was greatly molded. The cervix was 4 cm. dilated and partially effaced. There was secondary uterine inertia. An extraperitoneal cesarean section was done under continuous spinal anesthesia and a living full-term male infant delivered. The uterus contained pus which showed a pure culture of *Hemophilis influenzae*. The highest temperature postoperatively was 103° F. and there was a low-grade fever for five days, with only mild drainage for five days. She was discharged in good condition on the twelfth postoperative day.

1. Labor over twenty-four hours
2. Ruptured membranes over twenty-four hours
3. Attempts at delivery by forceps or version
4. Induction of labor by bag, bougie, or pack
5. Evidence of uterine infection
6. More than six vaginal examinations
7. More than twelve rectal examinations
8. Dead or damaged fetus

Few would disagree with many of these contraindications, but there is definitely a divided opinion as to how to manage patients who have gone beyond the criteria mentioned. Dieckmann⁶ states that such patients should be treated by embryotomy or cesarean hysterectomy when normal vaginal delivery is not possible. The proponents of extraperitoneal cesarean section state that this approach was devised in order to allow suprapubic delivery in infected cases, such as violate these criteria, without possible soiling of the peritoneal cavity and subsequent development of peritonitis. This division of opinion regarding cesarean hysterectomy, embryotomy, extraperitoneal cesarean section, and possibly transperitoneal section with large doses of antibiotics and chemotherapy has prompted the author to review the results obtained in such cases when treated by extraperitoneal technique.

Three personal series of consecutive cases of extraperitoneal cesarean section done in Philadelphia within the last few years were reviewed. It was found that the majority of operations were done upon patients after several or all of the criteria set by Dieckmann had been violated.

TABLE I

TOTAL CASES		EXCEEDING CRITERIA	FETAL MORTALITY	MATERNAL MORTALITY
Paxson	20	9	0	0
Briscoe ⁷	37	30	5	0
McCall	34	25	3	0
Totals	91	64	8	0

There was no maternal mortality. The fetal mortality was 8.8 per cent, and 9.4 per cent of the cases exceeding the criteria had babies who died of infection or the result of prolonged labor.

In the group of cases exceeding the criteria, it was evident that there were some patients who were extremely ill from the effect of far-advanced intra-uterine infection. Rather than dwell upon the over-all picture of extraperitoneal section and technique, it was thought that a more critical résumé of these badly infected cases would be more significant, since such cases present the most adverse conditions with which to test any procedure used in treatment.

Case Reports

CASE 1.—(Philadelphia General Hospital.) A 29-year-old Negro, gravida i, para 0, at term, was first seen after 99 hours of labor and 33½ hours of ruptured membranes. She was very toxic and psychotic with a fever of 103° F. and pulse of 170. Labor pains were five minutes apart and the uterus was tense and tender. Fetal heart tones were still present. The baby, in left occipitoposterior position, had a greatly molded head extending down to

After a total of 30 hours' labor and 100 hours ruptured membranes, a temperature of 101.4° F. developed, with a pulse of 130. The patient was toxic and obviously infected, with a tender uterus and foul vaginal discharge. Left occipitoanterior at minus one station with cervix 3 cm. dilated. X-ray showed much molding of head without engagement. Extraperitoneal section was done under continuous spinal anesthesia. The lower uterine segment was so thin that it ruptured during the usual retraction. The amniotic fluid was foul and under pressure. A normal full-term male child was delivered. The temperature became normal on the fifth day and there was no further draining from the lower angle of the incision after that time. She was discharged in good condition on the eleventh postoperative day.

CASE 10.—(Philadelphia General Hospital.) A 17-year-old Negro, gravida i, para 0, at 39 weeks' gestation, was seen after 87 hours of labor and 86 hours of ruptured membranes. The head had rotated completely posterior and was markedly molded in a small pelvis. The vertex extended 1 or 2 cm. below the spines. The cervix was thick and only 3 cm. dilated. Vaginal manipulation with attempt at manual dilatation and rotation has been done. The patient was ill and weak. The uterus was tense and tender. There was secondary uterine inertia and a purulent malodorous vaginal discharge. Penicillin had been given in adequate dosage for 72 hours but the patient was rapidly becoming increasingly toxic with signs of uterine infection. The temperature at the time of operation was 100.2° F. Extraperitoneal section under continuous spinal anesthesia was performed. A living 5 pound, 12 ounce girl was delivered. The fever went no higher and there was an uneventful recovery. Discharged on tenth postoperative day.

CASE 11.—(Philadelphia General Hospital.) A 23-year-old white, gravida i, para 0, at term, was placed in a room adjacent to her physician's office during the early part of labor. While there she was frequently examined vaginally by the doctor who, according to the patient, never wore gloves and always washed his hands afterward, not before. After twenty-four hours of labor, the patient was anesthetized and a version attempted, which failed. Several attempts were then made to deliver her with forceps but these kept slipping off. An ambulance was called and she was taken to the hospital in shock, undelivered. In the hospital, with the aid of transfusions and other supportive therapy, her condition improved. Examination revealed the baby to be in brow presentation, the head floating. Fetal heart sounds were not heard. The cervix was not completely dilated and there was a foul discharge. The pelvis was contracted. A complete tear was present through the sphincter of the anus into the rectum. There was also perforation in the bladder just below the urethra. This was closed and an extraperitoneal section done under continuous spinal anesthesia, the patient's general condition having revived remarkably. A 6 pound 1 ounce stillborn male with multiple skull fractures was delivered. The amniotic fluid had a foul odor. The third degree tear was also repaired. The patient responded very well. The highest temperature was 102° F., although there was some low-grade fever for seven days and some drainage from the incision for five days. Discharged on sixteenth postoperative day. There have been two subsequent operations for repair of the vesicovaginal fistula. The last one was successful.

CASE 12.—(Pennsylvania Hospital.) A 37-year-old white, gravida vi, para iv, at term. Had small babies in the past. After 60 hours of labor and 48 hours of ruptured membranes, the head was not engaged but was molded tightly into the upper pelvis with over-riding at the symphysis, 8 cm. dilatation of the cervix. High forceps were attempted but failed. There was a temperature of 100° F. and pulse of 110. An extraperitoneal cesarean section was done under continuous spinal anesthesia and an 8 pound 5 ounce female infant, which died shortly thereafter, was delivered. The postoperative course was hectic and there was fever for thirty-six days, the highest level being 104.8° F. There was evidence of bilateral pelvic thrombophlebitis during this time. The patient recovered and was discharged on the forty-eighth day following her operation.

CASE 5.—(Philadelphia General Hospital.) A 33-year-old Negro, gravida i, para 0, at term, was seen after 120 hours of labor and 105 hours of ruptured membranes. She had a temperature of 102° F., with a pulse rate of 120. Intrauterine death had taken place several days before and because clinical measurements and x-ray showed no disproportion, spontaneous delivery had been contemplated. In spite of penicillin therapy for 48 hours, the patient became critically ill with signs of intrauterine infection. The vertex was at zero and the thick cervix was only 2 cm. dilated. The uterus was tense and discharge foul. An extraperitoneal cesarean section was done under continuous spinal anesthesia and an 8 pound, 3 ounce stillborn macerated male child removed from the pus-filled uterus. The highest temperature postoperatively was 103° F. and there were five days of low-grade fever. There was drainage from the drain area in the incision for seven days. The patient was discharged in good condition on tenth postoperative day.

CASE 6.—(Philadelphia General Hospital.) A 33-year-old Negro, gravida i, para 0, at term, was seen after 108 hours of labor and 65 hours of ruptured membranes. Examination revealed a very tired patient with a temperature of 100.4° F. and pulse 110. The uterus was tender. Fetal heart sounds were present and there was a foul vaginal discharge. X-ray revealed an android type pelvis. The unengaged head was jammed into the superior strait and the caput extended to within 1 cm. of the spines. The cervix was 5 cm. dilated and 50 per cent effaced. An extraperitoneal cesarean section was done under continuous spinal anesthesia. The amniotic fluid was foul and thick. A living girl, weighing 5 pounds, 13½ ounces was delivered. The postoperative course was uneventful, the highest temperature being 100.4° F. Patient was discharged in good condition on thirteenth postoperative day.

CASE 7.—(Episcopal Hospital.) A 40-year-old white woman, gravida iii, para i, at 32 weeks' gestation, was seen after 100 hours of ruptured membranes. There were no pains. The first pregnancy had been terminated with high forceps after accouchement forcé and the fetus was stillborn. This was followed by a trachelorrhaphy because of residual cervical pathology. The second pregnancy was terminated in much the same manner with the aid of Dührssen's incisions after premature rupture of the membranes. This child was living but had been mentally inferior. In the present pregnancy, after rupture of the membranes, several medical inductions had failed. These were followed by four vaginal examinations with some manipulation of the cervix. When seen by the operator there was a foul vaginal discharge, a floating premature breech with heart tones present and no dilatation of a scarred cervix. There was a temperature of 100° F. and pulse 108. The uterus was slightly tender and the patient had suddenly become quite weak and langorous. An extraperitoneal cesarean section was done under continuous spinal anesthesia and a 4 pound 12½ ounce normal living girl delivered. The amniotic fluid was thin but very foul in odor. The highest temperature postoperatively was 101° F. and there was low-grade fever for five days. Patient was discharged in good condition on the thirteenth postoperative day.

CASE 8.—(Episcopal Hospital.) A 33-year-old white, gravida i, para 0, at term, was seen after 25 hours of labor and ruptured membranes for 72 hours. Left occipitoposterior at zero station with 4 cm. dilatation of a thick cervix. The patient was tired and toxic and the uterus was tense and tender. Examination revealed a funnel pelvis with contracted outlet. Temperature was 100.4° F. and pulse 104. A foul purulent vaginal discharge was evident. Under continuous spinal anesthesia an extraperitoneal section was done and a living full-term child delivered. The amniotic fluid was thick and gave forth an offensive odor. The highest temperature post partum was 101.4° F. There was purulent drainage from the lower angle of the incision for six days. She was discharged in good condition on eleventh postoperative day. Twenty-one months later a second child was delivered by elective cesarean section.

CASE 9.—(Jefferson Hospital.) A 26-year-old Negro, gravida i, para 0, at term, entered hospital in labor after membranes had ruptured at home three and one-half days before.

the vagina and the uterus was tender and tense. The head was not engaged and the diagonal conjugate measured 7.5 cm. An extraperitoneal section was done and a 6 pound 12 ounce living male infant delivered amid a gush of foul fluid. Upon the baby's head was an area which resembled a decubitus ulcer. The temperature at this time was 102.4° F. The fever lasted for six days but never went higher. There was a wound abscess. The patient was discharged on the twenty-second postoperative day. Three years later the patient, again at full-term pregnancy, allowed labor to start at home in spite of warnings. Upon entering hospital, a section was done and ruptured uterus found along the left broad ligament. The old incision was intact. A living child was delivered and a hysterectomy done. Recovery was complete.

Comment

Such cases as these should not exist in this so-called enlightened day of obstetric achievement. This paper in no way upholds the management of these cases before they became infected or up until the time of delivery. It does, however, uphold the method of delivery by extraperitoneal cesarean section after the condition was recognized. While the maternal mortality in this series was zero, it is not intended to imply that such a record could go on indefinitely. There is an irreducible minimum mortality rate for every major surgical procedure.

How would those who decry the efficacy of extraperitoneal cesarean section have treated these cases?

Recently Settle and Wilson⁸ have proposed that transperitoneal section with instillation of large amounts of sulfathiazole into the uterus, beneath the bladder flap, and in the peritoneal cavity is a method with which to treat potentially infected labor. There were no cases described which were as actually infected as the ones reported in this communication. A number of our cases upon whom extraperitoneal section was done had had penicillin and sulfonamide therapy for several days before becoming critically ill from infection. Another drawback to this method is the peritoneal irritation and the development of very tight adhesions which not only make subsequent surgery more difficult, but also give rise to the potential danger of intestinal obstruction and other alterations in intraabdominal physiology.

The only other methods are cesarean hysterectomy or embryotomy and, as has been pointed out, there are those who believe these methods should be used in exclusion of extraperitoneal cesarean section. In view of the evidence here presented, as well as that brought forward by others, it is hard to believe such a stand is any longer tenable.

It is occasionally good judgment to do a craniotomy on a dead baby if an easy delivery is made possible that way. The performance of a difficult embryotomy in a woman toxic and weakened by a long, fatiguing labor, as well as serious intrauterine infection, is another matter entirely, and it appears to the author to be outmoded and reprehensible even though the fetus be dead. Many

Footnote: Cases 12 to 18 were operated upon by Dr. C. C. Briscoe. Case 11 was furnished by Dr. J. Marsh Alesbury. Cases 1 to 10 were operated upon by the author, six at the Philadelphia General Hospital on the service of Dr. John C. Hirst, three were private cases done in consultation at the Episcopal Hospital, and one was done at the Jefferson Hospital on the service of Dr. Thaddeus L. Montgomery.

CASE 13.—(Pennsylvania Hospital.) A 31-year-old white, gravida i, para 0, was seen after 44 hours of labor and 34 hours of ruptured membranes. The patient was ill from the toxemia of infection. The uterus was tense and tender. There was a putrid vaginal discharge. The head was not engaged and there was obvious cephalopelvic disproportion. Temperature was 101.4° F., pulse 112. Extraperitoneal section was done under continuous spinal and a 6 pound 1 ounce normal living male infant delivered. The patient responded well after this, but developed wound infection with a temperature of 102° F. for three days. Discharged on fourteenth postoperative day.

CASE 14.—(Pennsylvania Hospital.) A 29-year-old white, gravida i, para 0, at term, was seen after an attempt to deliver by high midforceps had failed. She had been in labor 58 hours with ruptured membranes for 68 hours. The cervix was almost completely dilated. The abdomen was tender over the uterus and quite tense. A large baby was present and the fetal heart tones were still present. There was a malodorous purulent vaginal discharge and the patient appeared to be ill and toxic from infection. The temperature was 101° F. and the pulse 124. A 9 pound 8 ounce normal living female infant was delivered by extraperitoneal cesarean section under continuous spinal anesthesia. The patient responded well after operation and the highest temperature was 102.4° F. There was a temperature between 99° and 100° F. for ten days postoperatively. Discharged on eleventh postoperative day in good condition.

CASE 15.—(Pennsylvania Hospital.) A 21-year-old white, gravida i, para 0, at term, with a border-line pelvis, had had an attempted delivery with midforceps, which failed. She had been in labor for 50 hours with ruptured membranes. The vertex was at zero station and there was a rim of cervix remaining. The temperature was 101.4° F. and pulse 122. There was a foul vaginal discharge and the patient was worn out. A normal full-term child was delivered by extraperitoneal cesarean section under continuous spinal anesthesia. The highest temperature after this was 101.4° and there were nine days of low-grade fever. She was discharged in good condition on the fourteenth postoperative day.

CASE 16.—(Pennsylvania Hospital.) A 23-year-old Negro, gravida i, para 0, at term, had been in labor with ruptured membranes for 59 hours. There was cephalopelvic disproportion and the head was unengaged. The uterus was tender and there was secondary uterine inertia. The fetal heart sounds were present. There was an odorous vaginal discharge and the patient looked quite ill. Temperature was 100.4° F., pulse 120. An extraperitoneal section under continuous spinal anesthesia was done and a 7 pound 8 ounce living male child delivered. There was a temperature of 103° F. postoperatively and a wound abscess developed which caused a low-grade fever for fourteen days. Discharged in good condition on the nineteenth postoperative day. Sixteen months later a second child was delivered by elective section.

CASE 17.—(Pennsylvania Hospital.) A 26-year-old Negro, gravida i, para 0, at term, had been in labor 31 hours and membranes had been ruptured for 44 hours. The uterus was tender and tense but fetal heart tones were still present. There was a foul discharge and the vertex was found to be high above the spines and overriding at the symphysis. There was 4 cm. dilatation of the cervix. The temperature was 102.4° F. and pulse 128. An extraperitoneal section under continuous spinal anesthesia was used to deliver a normal living 6 pound 3 ounce male infant. There was pus under pressure in the uterus. There was a temperature of 104° F. after this surgery and a mild incisional infection developed. Fever lasted for nine days. The patient was discharged on the eleventh postoperative day in good condition.

CASE 18.—(Pennsylvania Hospital.) A 28-year-old Negro, gravida iii, para 0, at term, came into the hospital after 72 hours of hard labor at home. The membranes had been ruptured 24 hours. Many unsterile vaginal examinations had been made in the home. The patient was tired and toxic and obviously infected. There was a foul discharge coming from

soiling and the little trauma of the procedure; and the drainage of the tissues confluent with the parametrium which are reputed to be poorly resistant to infection and which are usually involved in the patient with puerperal fever.

The fact that women with the foulest of infections may be delivered safely by this method, all the while preserving the child-bearing organ, truly marks the newer technique of extraperitoneal cesarean section as a significant advance in modern obstetrics which should be recognized by all obstetricians until some simpler method, not yet known, appears to take its place.

Summary

1. 38 per cent of all cesarean section deaths are due to infection and usually follow transperitoneal operations done upon cases which have violated certain important criteria.

2. There is disagreement over the best method for delivery of the infected patient who cannot be delivered vaginally of an intact infant. The difference of opinion lies between cesarean hysterectomy, embryotomy, extraperitoneal cesarean section and transperitoneal cesarean section with local administration of sulfonamides.

3. Infected cases treated by extraperitoneal cesarean section are reported without maternal mortality.

4. Transperitoneal cesarean section in infected cases is pointed out as dangerous even though advantage is taken of the modern antibiotics and chemotherapeutic agents.

5. Difficult embryotomy is pictured as being outmoded and reprehensible.

6. Cesarean hysterectomy is criticized as being a mutilating and dangerous procedure when used in primigravidas, even though severe intrauterine infection is present.

7. The modern technique of extraperitoneal cesarean section is the safest and simplest method of treating severely infected cases when vaginal delivery of an intact infant cannot be consummated.

Note: The author wishes to express his appreciation to Dr. Newlin Paxson, Dr. Clarence Briscoe, and Dr. J. Marsh Alesbury for allowing the inclusion of their cases in this paper.

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decades ago, difficult embryotomy was necessary because of the high mortality of cesarean section and the obstetricians of that day were undoubtedly much better technicians in its performance because of this. Today, very few indeed have developed this degree of competence.

Cesarean hysterectomy was originally devised to reduce the frightful mortality from infection associated with cesarean section. Today the indications for this procedure have widened and include ruptured uterus, intractable hemorrhage, Couvelaire uterus, uterine myomas, placenta accreta and, in some hands, as a method of sterilization. Moreover, textbooks still almost invariably mention intrauterine infection as an indication.

Reis and De Costa,⁹ in their recent article, reviewed 731,690 deliveries reported from well-known clinics in the American literature since 1939. Six hundred fifty-six cesarean hysterectomies were done with a mortality of 5.2 per cent, which was approximately two and one-half times as great as the cesarean section mortality of 2.14 per cent. The individual series had mortalities for this procedure of from zero to over 22 per cent.

It is our feeling that cesarean hysterectomy in foully infected patients is dangerous. Although hysterectomy upon the gravid uterus is often easy to perform, it is a shocking procedure to the dangerously ill, violently infected patient. The peritoneal cavity is invaded and peritonitis is still liable to develop even though the uterus is removed. A condemning feature of this operation is the sacrifice of the uterus in primiparas, for it is usually the woman pregnant for the first time who has a prolonged infected labor. Of the eighteen patients mentioned here, fifteen were primigravidas.

Extraperitoneal cesarean section is not only much less traumatic and shocking than difficult embryotomy or hysterectomy, but also affords the fetus a chance of surviving and preserves the uterus. It is a simple incision of the uterus outside of the peritoneal cavity. It is well known that incision and drainage is one of the most efficacious procedures employed in surgery. The sulfonamides and antibiotics will not save a patient who needs drainage of pus under pressure. This has repeatedly been shown in general surgery, as well as in our series of profoundly infected cases of pregnancy, where extraperitoneal incision and drainage of the foully infected uterus have given excellent results. As has been shown, this operation is used at times when the fetus is known to be dead, and it appears that this traditional contraindication to cesarean section is no longer valid.

There have been numerous criticisms of extraperitoneal section technique, most of which lose significance after a little experience in doing the operation has been achieved. However, there is one which has not been definitely answered and we feel much as does Schumann,¹¹ who recently, at the American Congress of Obstetrics and Gynecology, remarked that he was "at a loss to explain why these patients with free pus in the uterine cavity yielding positive cultures of pyogenic bacteria do not go on and develop puerperal sepsis after extraperitoneal section."

That they do not is undoubtedly due to several factors, among which may be: the use of modern postoperative management; the prevention of peritoneal

delivering these patients. As has been pointed out, craniotomy is sometimes feasible if it can be done on the dead or damaged baby without increasing the maternal risk. It is preferable to making an incision in the uterus and asking the patient to have the rest of her babies by cesarean section. There is also a place for cesarean hysterectomy and I cannot agree that it is quite as formidable a procedure as has been suggested. The mortality rates presented for hysterectomy in the pregnant patient usually include the operations done for hemorrhage, ruptured uterus, etc., in addition to the true cesarean hysterectomy for infection, and consequently are distorted. We do not always know in which cases the uterus should be removed; it is difficult to tell. While these cases were without doubt badly infected. I would say that most of them were rather superficial infections of the uterus since the majority cleared up rapidly after delivery. The patient who has an infected uterus and myometritis with extensive abscess formation certainly is not going to do nearly as well, if the uterus is left, as these patients did. Many years ago, Baldwin reported a marked reduction in mortality in such patients by hysterectomy. The recent work of Falk in the treatment of septic abortions with widespread peritonitis by hysterectomy also suggests that this procedure is valuable, since the infections in each instance are comparable. I would hesitate to give up any one of the three methods of delivering these infected patients since it seems that no one procedure can be applied to every case.

DR. NEWLIN F. PAXSON.—I too have become enthusiastic concerning this operation. New processes have to be subjected to many analyses before they are part of a standard procedure. It seems to me we have gotten far enough along to realize that it should be part of the armamentarium of every large clinic. We teach at Hahnemann, in our ward cases, that all cases of labor needing cesarean section must have extraperitoneal cesarean and by that method we are training the junior staff obstetricians and residents. Our series is now up to some fifty cases plus and still no maternal deaths. We also teach that there is a place for craniotomy where the cervix is fully dilated. I am opposed to vaginal operation for delivery through an incompletely dilated cervix. When the cervix is dilated, or the baby is dead, or there is an aftercoming head, craniotomy is the better operation. We reserve cesarean hysterectomy for problems of uterine disease complicating pregnancy, fibroid, etc., but when we come to sepsis during labor we feel that extraperitoneal section has answered our needs more satisfactorily than any procedure so far.

DR. EDWARD A. SCHUMANN.—So far as I am aware, this is the first paper which describes the use of extraperitoneal cesarean section in a series of profoundly infected patients and one cannot avoid being deeply impressed by the fact that many of these patients would, in all probability, have been doomed to death by any form of intraperitoneal cesarean section. The postoperative course, even in these badly infected women, has been so smooth that one is impelled to the belief that, as soon as competency in performing this operation has become widespread, it will probably replace all other types of cesarean section even in the elective cases because, if the risk of intraperitoneal infection can be avoided by a technique not too involved, it follows that this precaution becomes almost automatic. With regard to hysterectomy following cesarean section, this operation has always been repugnant to me. It is a confession of abject defeat on the part of the physician in handling a complication of the reproductive function. Personally, I see no reason to perform hysterectomy following cesarean section except in a uterus obviously diseased beyond redemption. Multiple fibroids, profound infiltration with blood, extensive rupture, such conditions may warrant the removal of the organ but certainly not infection of a doubtful degree. Here the extraperitoneal cesarean section is the operation of choice. Cesarean section in the presence of a dead infant has been considered improper obstetrics but I feel very strongly that, in the event of a firmly impacted dead fetus, where embryotomy would involve the difficulties and traumatisms so often associated with this procedure, the extraperitoneal cesarean section is a far safer method of delivery. Difficult embryotomies are so uncommon that there are but few obstetricians who have developed the skill necessary to perform such an operation, particularly upon an exhausted and infected woman, without grave danger. Therefore, I feel that extraperitoneal section will solve many of these problems.

Discussion

DR. C. C. BRISCOE.—There has been a gratifying reduction in postcesarean sepsis recently; a result of such factors as earlier use of cesarean section, the prophylactic and active use of chemotherapeutic and antibiotic agents, the liberal replenishment of blood, and, when indicated, the exclusion of transperitoneal section and cesarean hysterectomy in favor of extraperitoneal abdominal delivery.

The failure of some clinics to adopt this procedure can be explained by their exclusive use of local anesthesia, an agent unsuited to extraperitoneal section. It would seem that some occasional desperate situations arise where minimal dose fractional spinal anesthesia might be used so that these babies, uteri, and lives could be saved.

These results should forever relegate to oblivion craniotomy on the living fetus. The reported 10 per cent fetal mortality is an eloquent plea for earlier section, but, even so, a ninety per cent fetal survival rate is considerably better than the absolute mortality obtained by craniotomy. Craniotomy on the dead fetus should be limited to cases of dystocia with the impacted head low in the pelvis, the hydrocephalic head low in the pelvis, and the aftercoming head. For inlet disproportion, extraperitoneal delivery is safer.

I fail to see why cesarean hysterectomy enjoys a good reputation as a means of treating infected women requiring abdominal delivery, for the reported mortality rate in all large series is about 10 per cent. It appears safer only by comparison with classical section under similar adverse conditions.

In both 1931 and 1941, cesarean hysterectomy accounted for ten per cent of the postcesarean septic deaths in Philadelphia, although less than two per cent of the sections performed were of this type. Most of these operations are done for uterine rupture, abruptio atony, or myomas, yet the mortality rate from sepsis alone was twenty per cent and 5.8 per cent, respectively, in these two years.

During the past fifteen years at the Lying-In Hospital, seven women had cesarean hysterectomy because of infection. Two died, another suffered severe generalized peritonitis for weeks, saved only by the grace of God and huge doses of penicillin. Of 315 cesarean hysterectomies, which I have collected, 85 were performed for infection and 15.2 per cent of these were fatal. This compares most unfavorably with the present mortality rate for extraperitoneal section of 1 per cent, and the prepenicillin rate of 3 per cent.

To know why these infected patients survive after extraperitoneal delivery, we must turn to the autopsy room. Frank, in his monograph, shows that most women who die of sepsis, following vaginal delivery, die from vascular extension of the endometrial infection, while only 23 per cent die of peritonitis. On the other hand, in 45 autopsies which I have studied, 80 per cent of the patients who died of sepsis following cesarean section succumbed from generalized peritonitis. Incidentally, generalized peritonitis was present in every patient who had been treated by hysterectomy. This means that the intact uterus usually confines its infection within the parametrium, unless there be vascular spread. On the other hand, transperitoneal section and cesarean hysterectomy permit gross intraperitoneal infective spill and subsequent leakage through suppurative suture lines. In the extraperitoneal section, original spill is avoided and subsequent suppuration is drained. From a growing experience with this operation, and these data I concur wholeheartedly with Dr. McCall's conclusions.

DR. J. ROBERT WILLSON.—I cannot quite agree with the previous discussant that the place of extraperitoneal section has been settled by this paper. It is, however, one of the very few papers that has presented any instructive material regarding the mortality rate in infected patients. The vast majority of reports have combined the sections done on infected patients, those done in potentially infected patients who might have been equally well handled by transperitoneal section, and those cases which were used simply for teaching material. If subsequent series such as Dr. McCall has presented show equally good results, it will certainly go a long way toward convincing some operators that it is a safe procedure. I do not think, however, we can discard completely the other methods of

A REVIEW OF 445 PREGNANCIES COMPLICATED BY FIBROMYOMAS

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ONE or more cases of fibromyomas and pregnancy are constantly present on the ward service at the Sloane Hospital. Since proper treatment continues to be the basis of discussion and dispute, it was considered of interest to review the records of recent years.

Incidence

Over 60,000 admissions to this hospital covering the period from its inception to 1931 have been reviewed and previously reported.

The present report covers an additional 20,763 obstetric admissions during the years 1934 to 1945, inclusive. There were 392 cases with a total of 445 pregnancies with complicating fibromyomas—an incidence of 2.1 per cent. This incidence exceeds those quoted in the literature (Table II) and shows an increase over previous reports from this hospital (Table I). Better records and an increase in the number of Negro admissions may account for this. Of the present cases 261 (66 per cent) were Negroes.

TABLE I. INCIDENCE OF FIBROIDS AT SLOANE HOSPITAL

YEARS	AUTHOR	NO. OF CASES	NO. OF FIBROIDS	PER CENT
1886-1915	Craigin and Ryder	20,000	89	0.45
1916-1924	Pierson	30,836	250	0.8
1925-1931	Watson	11,675	157	1.3
1934-1945	Present Series	20,763	445	2.1

TABLE II. INCIDENCES QUOTED IN THE LITERATURE

AUTHOR	PER CENT
Mussey, R. D., and Hardwick, R. S.	1.9
Browne, F. J.	0.28
Kosmak, G. W.	0.34
Campbell, R. E.	0.43
Emge, L. A.	1.3
Eisaman, J. R.	0.3
Duckering, F. A.	1.4
Buckell, E. W. C.	0.79

Classification as to Significance

The significance of the fibromyomas was graded one plus to four plus, based on a combination of size, number, location, symptoms, and the opinion of the clinicians in charge.

The data in Table III reveal that 58 per cent of the cases were of significance.

DR. THADDEUS L. MONTGOMERY.—Dr. McCall's paper is of particular value because it goes a long way in helping to establish the efficacy of the extraperitoneal type of cesarean section in the treatment of the infected patient who requires abdominal delivery. The cases which he has gathered from his own experience, and from the experience of several other operators in Philadelphia who have performed the majority of these operations, were truly infected patients and answer fully the criteria which Dr. Dieckmann has suggested. The number of cases is not large because there are not too many patients who fall into this category in modern obstetric practice, but the results are all the more impressive because they truly represent what can be accomplished in obtaining low morbidity, low mortality, and preservation of the childbearing function in these cases.

I have often wondered why the extraperitoneal operation gives so much better results in the potentially infected or actually infected patient than the transperitoneal low cesarean section, because it is difficult to believe that a thin layer of translucent peritoneal tissue will act as a barrier to infection entering the peritoneal cavity. Also, it frequently happens that this peritoneum is nicked or traumatized in the course of operation and has to be closed, and quite likely there are abrasions or areas which are not recognized and permit of some access of fluid and bacteria into the peritoneal cavity. My own opinion is that actually the peritoneal cavity is possibly more resistant to infection than is the connective tissue of the parametrium and that the important factor in the extraperitoneal operation is the establishment of a tract for thorough drainage of the extraperitoneal field following operation. This thorough drainage plus the use of antibiotics provides for the protection of the peritoneal cavity from infection, in addition of course to the avoidance of any gross spill into the peritoneal cavity at the time of operation.

While there is still a place for the procedure of cesarean section and hysterectomy in certain infected patients and, of course, in not a few patients with neoplasms complicating pregnancy and various hemorrhagic conditions, yet the extraperitoneal operation of cesarean section has been found to have great value and has lessened the number of instances in which hysterectomy is essential.

DR. MCCALL (Closing).—The main purpose of the paper was to record as many cases as we had seen of truly infected patients. As to technique, I might mention in closing that in Dr. Paxson's and Dr. Briscoe's series, the supravescical technique of Waters was used exclusively. In my series, twenty-one were done by the latter technique and thirteen by the paravesical technique of Norton, where more blunt dissection is used. Both of these techniques are excellent, indeed, although the method of Norton has been used more often in the recent cases.

Eighty-five (21 per cent) of the patients had a total of 145 previous abortions. Six had a total of 13 induced abortions without any history of sepsis following. However, it is difficult to obtain an accurate history on the latter type of case.

The most that one can deduce from the above figures is that relative infertility exists in patients with fibromyomas.

Labor Time

The duration of labor was not increased in this series, nor was there any correlation between duration of labor and the significance of the fibroids. This is in contrast to a generally held opinion that fibromyomas increase labor time.

Table VI demonstrates the latter statement. Primiparous labors averaged 15 hours, 42 minutes and multiparous labors ten hours, six minutes. Of 307 labors, 35 (11 per cent) were cases of prolonged labor (greater than 30 hours) and 17 (5 per cent) were cases of precipitate labor (less than 3 hours). Campbell reported 26 per cent prolonged labors and 49 per cent of his cases with shorter labors than normal.

TABLE VI. DURATION OF LABOR IN RELATION TO SIGNIFICANCE AND PARITY

SIGNIFICANCE	PRIMIPAROUS LABORS		MULTIPAROUS LABORS	
	NO. CASES	AVERAGE TIME (HOURS AND MINUTES)	NO. CASES	AVERAGE TIME (HOURS AND MINUTES)
0	56	16:12	74	11:51
1-2 plus	77	15:45	76	9.20
3-4 plus	15	12:25	9	15:22
Average time per group		15:42		10:06

Size of Fibromyomas

As seen in Table VII, increased size of the fibroids was correlated with increased significance. Thus, of 187 cases of no significance, only 3 per cent were 6 cm. or more in diameter. Seven per cent of the 1 plus group, 51 per cent of the 2 plus, 60 per cent of the 3 plus and all of the 4 plus cases exceeded 6 cm. in diameter. In the groups of low significance, size is not a prime factor.

TABLE VII. THE SIZE OF THE FIBROIDS RELATED TO SIGNIFICANCE

SIGNIFICANCE	SIZE IN CENTIMETERS			
	2-2.9	3-5.9	6-9.9	GREATER THAN 10
0	106	76	5	0
1 plus	39	84	11	1
2 plus	4	28	32	2
3 plus	3	8	14	2
4 plus	0	0	20	10

In 53 cases, the fibroids increased in size during the antepartum course. A decrease in size post partum occurred in 104 cases. The fibroids that enlarged antepartum did not necessarily decrease in size after delivery.

There were 53 successive pregnancies recorded.

In Table VIII the course of fibroids as regards size is demonstrated in succeeding pregnancies. Emge contended that fibroid enlargement during pregnancy is temporary and that in subsequent pregnancies, fibromyomas occasionally enlarge or enlarge to a lesser degree. This series only partially agrees with Emge's conclusions.

TABLE III. NUMBER OF CASES IN RELATION TO SIGNIFICANCE

SIGNIFICANCE	NUMBER
0	187
1 plus	135
2 plus	66
3 plus	27
4 plus	30
Total "significant" cases	258

Age

The average age was 32 years. As shown in Table IV, about 75 per cent were over 30 years. This age distribution is in accord with the age incidence of fibromyomas in general. It is noted that the patients, aged 30 years and over, make up 75 per cent of the over-all groups as well as the individual groups subdivided as to significance. Age is not related to the degree of significance of the fibromyomas.

TABLE IV. AGE AS RELATED TO SIGNIFICANCE AND NUMBER OF PREGNANCIES IN DIFFERENT AGE GROUPS

AGE	SIGNIFICANCE					TOTAL	PER CENT
	0	1 PLUS	2 PLUS	3 PLUS	4 PLUS		
Less than 20	3	1	0	0	0	4	0.9
20-29	46	31	18	6	8	109	24.5
30-39	128	91	41	17	19	296	66.5
40-49	10	12	7	4	3	36	8.1
Total	187	135	66	27	30	445	

Parity and Gravidity

Two hundred twenty-seven (51 per cent) of the pregnancies occurred in primigravidas; 180 (40.5 per cent) had had one or two term pregnancies previously; the remaining 8.5 per cent had had more than two previous term pregnancies.

The data in Table V shows that parity and gravidity decreased inversely to the significance. However, in the cases of 0 to 3 plus significance, approximately 50 per cent had had a previous term pregnancy. The 4 plus group was marked by having 80 per cent primigravidas with only 13 per cent having had a previous term pregnancy.

TABLE V. PARITY AND GRAVIDITY AS RELATED TO SIGNIFICANCE

SIGNIFICANCE	P0	P1	P2	P3	P4	P5	P6	P7
0	84	56	23	12	7	1	3	1
1 plus	69	35	23	5	2	1	0	0
2 plus	34	21	7	2	1	1	0	0
3 plus	14	6	5	1	1	0	0	0
4 plus	26	4	0	0	0	0	0	0
Total	227	122	58	20	11	3	3	1

SIGNIFICANCE	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11	G12
0	70	57	36	13	1	3	4	1	0	1	0	1
1 plus	51	31	20	19	7	4	3	0	0	0	0	0
2 plus	27	16	9	9	0	3	1	1	0	0	0	0
3 plus	10	5	7	2	2	1	0	0	0	0	0	0
4 plus	24	5	0	1	0	0	0	0	0	0	0	0
Total	182	114	72	44	10	11	8	2	0	1	0	1

Ten per cent of the cases were operated upon ante partum.

The operations and the indications are listed in Table XI. Of the three myomectomies, only one continued to term to be delivered by cesarean section. One of the laparotomies for ovarian cyst proved to be an error in diagnosis, a fibroid was present.

TABLE XI. OPERATIONS WITH INDICATIONS ANTE PARTUM

OPERATION	NO.	INDICATION	NO.
Hysterectomy	18	Fibroids	6
		Degenerating fibroids	2
		Fibroids and hypertensive vascular disease	5
		Fibroids and pyelonephritis	1
		Fibroids and toxemia	1
		Fibroids and exophthalmic goiter	1
		Fibroids and anxiety neurosis	1
		Fibroids and undiagnosed pulmonary disease	1
Dilatation and curettage	16	Incomplete abortion	12
		Therapeutic abortion	4
Myomectomy	3	Fibroids	3
Myomectomy and hysterotomy and sterilization	4	Fibroids and hypertensive cardiovascular disease	3
		Fibroids and Boeck's sarcoid	1
Myomectomy and hysterotomy	1	Fibroids and rheumatic heart disease	1
Appendectomy	1	Acute appendicitis	1
Laparotomy for ovarian cysts	2	Ovarian cyst	2
Total	45		

Labor

The data in Table XII show the presentation present at term or during labor. The malpresentation incidence was two to three times the stated average incidence.

TABLE XII. PRESENTATION AT TERM AND DURING LABOR

PRESENTATION	NUMBER
Vertex	355
Breech	28
Twins	6
Transverse	1
Face	3

TABLE XIII. COMPLICATIONS OF LABOR

COMPLICATIONS	NUMBER	PER CENT
Premature rupture of membranes	106	21.0
Premature delivery	14	3.1
Uterine inertia	32	7.2
Dry labor	0	0
Mechanical obstruction	6	1.3
Prolapse of cord	6	1.3
Retained placenta	8	1.8
Prolonged labor (more than 30 hours)	35	11.0
Precipitate labor (less than 3 hours)	17	5.0
Postpartum Hemorrhage	19	4.3

During the antepartum course, 72 per cent of the fibroids were first noted; 19 per cent were noted the first time at term and 9 per cent first diagnosed post partum. The greater the size of the fibroids, the earlier the time of detection.

TABLE VIII. COURSE OF FIBROIDS IN SUCCESSIVE PREGNANCIES

SUBSEQUENT PREGNANCIES	NO. OF CASES
No change in size	32
Increased size	10
Decreased size	11
Total	53

Degeneration of Fibroids

Only one of four fibromyomas evidenced degeneration. Degeneration was variable in successive pregnancies. Of the cases that degenerated in the first pregnancy, 6 per cent did not degenerate subsequently, whereas 10 per cent that did not evidence degeneration in the first pregnancy did degenerate in later ones.

Antepartum Course

Table IX reviews the antepartum course. One hundred and twenty-five (28 per cent) had pain of varying degrees. In the 53 successive pregnancies, 15 per cent had pain in first pregnancies and none subsequently, whereas 7.5 per cent had no pain in first pregnancies, but did have pain in following ones.

TABLE IX. COMPLICATIONS OF ANTEPARTUM COURSE

SIGNS, SYMPTOMS, AND PATHOLOGY	NO. OF CASES
Pain	125
Bleeding	50
Fever due to fibroids	4
Varices (vulval and extremities)	8
Urinary obstruction	2
Respiratory and cardiac distress	2
Toxemia	46
Hypertensive vascular disease	24
Torsion of fibroids	0
Infection of fibroids	0
Early abortions	8
Late abortions	14

Sedimentation rates were not recorded constantly enough to be evaluated.

The abortion rate of the 445 cases herein reported was 5 per cent, a low rate compared to the usual estimate of the "normal" rate of abortion which is about 20 per cent.

The toxemia and hypertension incidence was 10 and 5 per cent, respectively—the same as the generally prevailing rate.

No fibroids became infected ante partum but three did post partum.

Table X demonstrates that hemoglobin values are unaffected by the fibromyomas. The higher hemoglobin values in the more severe cases are not significant.

TABLE X. AVERAGED HEMOGLOBIN VALUES ANTE PARTUM

SIGNIFICANCE	HGB. PER CENT
0	77.5
1-2 plus	79.5
3-4 plus	85.0

TABLE XVI. OPERATIONS AT TERM

OPERATION	NUMBER	PER CENT
Cesarean section	95	61.3
Low forceps	20	12.9
Midforceps	9	5.8
Assisted breech	25	16.1
Version-breech extraction	2	0.65
Dührssen's incisions	1	0.65
Manual removal of placenta	1	1.23
Craniotomy	2	1.23
Total	155	

The indications for cesarean section are listed in Table XIV. It is noted that many of the indications were multiple, leaving only 14 with dystocia due to myoma, 7 with degenerating fibroids, and 5 elderly primiparas with fibroids as the sole indications for section. Another 35 had sections primarily for reasons exclusive of fibroids.

Morbidity

Of the 445 cases, 118 (26 per cent) had a postpartum or postoperative morbid course. This morbidity rate is three times the eleven-year average incidence at Sloane.

A review of Table XVII shows that the highest operative morbidity is associated with cesarean section, the lowest with cesarean section plus myomectomy. The morbidity for cesarean and supravaginal hysterectomy, though far below that of cesarean sections, is above that for cesarean and myomectomy. Huber and Hesseltine claimed that cesarean plus supravaginal hysterectomy yielded the lowest morbidity. This series does not support the latter contention. There would appear to be no contraindication to doing myomectomy as far as morbidity is concerned.

TABLE XVII. MORBIDITY RATE FOR DIFFERENT MODES OF DELIVERY

MODE OF DELIVERY	NO. CASES	PER CENT MORBIDITY
Spontaneous	247	14.7
Forcep and breech	54	48.8
Cesarean section	20	85.0
Cesarean section and myomectomy	28	42.1
Cesarean section and supravaginal hysterectomy	43	48.8

About 10 per cent of the total cases exhibited subinvolution post partum.

The mortality rate was 0.6 per cent. In Cases A and B in Table XVIII, fibromyomas were important causative factors.

TABLE XVIII. SUMMARY OF FATALITIES

Case A.—Spontaneous delivery; subsequent intestinal obstruction due to adhesions between a fibroid and sigmoid.
Case B.—Prolonged labor, midforceps, peritonitis secondary to degenerating fibroid.
Case C.—Therapeutic abortion and sterilization for hypertension and fibromyomas; postoperative intestinal obstruction.

Fetal Mortality

As indicated in Table XIX, the over-all fetal mortality is high. Early, late, and therapeutic abortions are the prime contributors to the high rate. If, among the neonatal deaths, the three so-called previable births are excluded, a corrected fetal mortality rate of 36 per thousand is obtained, which is comparable to the corrected fetal mortality rate for all pregnancies at this hospital.

The absence of fetal mortality following cesarean section is noteworthy.

A list of the complications of labor is presented in Table XIII. The incidence of premature delivery is not excessive. Prolapse of the cord occurred with average incidence; in four of the cases the prolapse was attributed to malpresentation. Postpartum hemorrhage occurred with less than the usual incidence, whereas retained placenta occurred twice as often.

Delivery

Four hundred two cases, 90 per cent of the recorded pregnancies, came to delivery. Of these, 247 (61 per cent) delivered spontaneously.

One hundred fifty-five (39 per cent) were operative deliveries. Of the latter, 95 were cesarean sections.

The section rate for term pregnancies was 21.3 per cent. If correction is made to include only those cases where fibromyomas made up the whole or part of the indication, the rate was 12.8 per cent. See Table XIV.

TABLE XIV. INDICATION FOR CESAREAN SECTION

INDICATION	NO. CASES	NO. CASES WITH MULTIPLE INDICATIONS
Dystocia due to myoma	26	12
Painful or degenerating fibroids	12	5
Elderly primiparas with fibroids	20	15
Disproportion	39	21
Elderly primiparas with sterility	4	3
Elderly primiparas with poor labor	4	3
Previous section or myomectomy	18	9
Elderly primiparas with breech	2	2
Eclampsia	0	0
Severe pre-eclampsia	3	2
Premature separation of placenta	2	0
Placenta previa	3	0
Chronic nephritis	0	0

Of the 95 sections, 26.3 per cent were classical, 28.2 per cent low flap, 45.3 per cent cesarean plus supravaginal hysterectomy and 1.1 per cent Latzko extra-peritoneal section. Table XV further analyzes the sections.

Of the twenty-four patients who had myomectomies, eleven subsequently became pregnant again, ten delivering by repeat sections and one delivering spontaneously.

TABLE XV. CESAREAN SECTIONS

TYPE OPERATION	NUMBER	PER CENT
Classical	5	5.26
Classical and myomectomy	14	14.73
Classical and myomectomy and sterilization	2	2.10
Classical and sterilization	4	4.20
Low flap	15	15.77
Low flap and myomectomy	10	10.52
Low flap and sterilization	2	2.10
Cesarean with supravaginal hysterectomy	43	45.26
Latzko extraperitoneal	1	1.05

Table XVI reviews the operative procedures used in the course of delivery.

The antepartum and term operative procedures totaled 200 or 44.9 per cent of the recorded pregnancies. Compared to the operative incidences of 48 per cent and 46.5 per cent as reported by Watson and Pierson at Sloane, there has been no significant diminution through the years.

Forty-four (10 per cent) of the patients were operated upon in antepartum courses. Of these, 40.9 per cent had hysterectomies and 18.1 myomectomies. Three of the latter had myomectomies only and, of these three, only one continued to term and was terminated by section.

Malpresentations occurred with two to three times the usual incidence. There were 14 premature labors, an incidence of 3.1 per cent—about average.

Postpartum hemorrhage in 19 cases showed an incidence of 4.3 per cent. This is less than the usual incidence for all pregnancies. Retained placenta occurred eight times, an incidence of 1.8 per cent—twice the usual incidence. Ninety per cent of the cases came to delivery; of these, 247 delivered spontaneously and 155 were operative deliveries. Of the latter, 95 were cesarean sections, 29 were forceps deliveries. Nine, or 31 per cent, of the forceps were of the midforceps variety. The total operative incidence equalled 44.9 per cent—about the same as previously reported at this hospital.

Of 24 patients on whom myomectomies were performed, 11 subsequently became pregnant; 10 delivered by section, 1 spontaneously.

The cesarean section rate was 21.3 per cent. Corrected for fibroids as part or the whole of the indication, the rate was 12.8 per cent.

The morbidity rate was 26 per cent. This is three times the usual rate at Sloane. The morbidity rate for cesarean plus myomectomy was lower than that for cesarean hysterectomy. On the basis of morbidity there appeared to be no contraindications to cesarean plus myomectomy. Morbidity remains a prominent feature of fibromyomas and pregnancy.

Three patients died, a mortality rate of 0.67 per cent. This is a significant rate but lower than previously reported at Sloane.

If therapeutic abortions and spontaneous abortions are included, the fetal mortality is 150 per thousand. Corrected for viable fetuses, the rate becomes 36 per thousand—comparable to our over-all fetal mortality rate.

The rate of postpartum subinvolution was 10.3 per cent. The average hospital stay was 14½ days. Thus, fibroids become economically and administratively important.

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Hospital Days

The average stay in the hospital was 14.5 days. Thus, fibromyomas are also an important economic and administrative factor.

TABLE XIX. FETAL DEATHS AND ACCOMPANYING METHOD AND TIME OF DELIVERY

METHOD AND TIME OF DELIVERY	NUMBER
Early, late, and therapeutic abortions	43
Miscarriage (20 to 28 weeks)	8
Stillborn	7
Neonatal	
24 weeks, spontaneous	1
20 weeks, spontaneous	1
18 weeks, spontaneous	1
Term, spontaneous	2
Term, assisted breech	1
Term, spontaneous breech	1
Term, midforceps	1
Cranioclast	1
Uncorrected fetal mortality rate	150/M
Corrected fetal mortality rate	36/M

Comment and Summary

A review of 20,763 obstetric admissions is presented. Of these, 445 had complicating fibromyomas, an incidence of 2.1 per cent. Two hundred fifty-eight were rated as significant. Significance was graded from one plus to four plus.

The average age of the patients was 32 years. Seventy-five per cent of the patients were over 30 years of age. Age and degree of significance did not correlate. Parity and gravidity decreased as the significance increased. This was most marked in the cases of four plus significance. Fifty-one per cent of the patients were primigravidas. Relative infertility and fibroids seemed to go hand in hand.

Labor time was not prolonged by fibroids. Primiparas averaged 15 hours, forty-two minutes and multiparas ten hours, six minutes.

Fibroid enlargement in pregnancy is frequently but not always temporary. Only one of four fibroids evidenced degeneration. Degeneration was variable in multiple pregnancies. Six per cent of the cases that degenerated in the first pregnancy did not degenerate subsequently. Ten per cent that did not evidence degeneration in the first pregnancy did degenerate subsequently.

During the antepartum course, 28 per cent complained of pain. Of the successive pregnancies, 15 per cent had pain in the first pregnancy, none in subsequent pregnancies. Four, or 7.5 per cent, had no pain in the first pregnancy but pain in subsequent ones. Eleven per cent had varying degrees of bleeding. Hemoglobin levels were unaffected by the fibromyomas.

Five per cent of the cases aborted, a very low abortion rate. Toxemia and hypertensive disease showed an incidence of 10 and 5 per cent, respectively, the same as the generally prevailing rates.

Comparisons of the determined versus the calculated hemoglobin concentration indicated that the mean error in the clinic laboratory was 0.6 Gm. and in the chemistry laboratory 0.28 Gm. The normal standard for women is hemoglobin, 14.3 Gm., hematocrit, 43 per cent (heparin), and erythrocyte, 5 million.

Any patient who is less than twelve weeks pregnant or more than six weeks post partum whose hematocrit is less than 37 volumes per cent (12.0 Gm. per cent) is referred to the antepartum anemia clinic. Between twelve weeks and thirty-six weeks' gestation, the lower limit of the hematocrit is 30 (10 Gm. per cent), and between thirty-six weeks and term the lower limit is 32 volumes per cent (10.5 Gm. per cent). The procedure in the anemia clinic is to obtain additional history and special examinations as to possible causes for the anemia. A diet history is obtained in some instances. The hemoglobin, hematocrit, red-cell count, leucocyte count and differential determinations are made. The various indices, mean corpuscular hemoglobin concentration and individual cell volume, etc., are determined and the anemia classified. All cases complicated by blood loss, toxemia, and infection were excluded in this study.

After a preliminary observation period of two to six weeks during which the determinations were repeated, therapy was begun. A capsule containing 3.0 mg. of molybdenum sesquioxide (approximately 2.5 mg. molybdenum) and 195 mg. of ferrous sulphate (approximately 40 mg. iron) was given to these patients (2 capsules three times a day, after meals). They contained no significant amounts of copper. Complete blood studies had been made and the hemoglobin, hematocrit, and red blood count were repeated every two weeks.

Data given in Table I show the percentage of patients with hemoglobin concentrations for our 1936 (3 yrs. 8 mos.) report and for a recent group (1 year) of patients from our clinic. It is obvious that there is a marked decrease in the number of anemic patients both in the clinic and private patient groups. Patients are not routinely given iron in any form. The only vitamin preparation is one containing A and D. The income of our patients is much higher today than it was in the period from 1933 to 1936. Considerable pressure is put upon each patient to see the dietitian but that does not mean that every patient does so nor does it mean that every patient follows the outlined diet.

TABLE I. FREQUENCY DISTRIBUTION OF HEMOGLOBIN CONCENTRATIONS IN PREGNANT PATIENTS

HEMOGLOBIN GM. PER 100 ML.	STAFF PATIENTS PER CENT		PRIVATE PATIENTS PER CENT	
	1936	1948	1936	1948
5- 5.9	0.06	0.03	0	0
6- 6.9	0.4	0.03	0	0
7- 7.9	1.0	0.28	0	0.08
8- 8.9	3.0	1.1	1.2	0.71
9- 9.9	7.0	3.2	5.9	2.8
Per cent of patients less than 10 gm. per cent	11.5	4.6	7.1	3.6
10-10.9	20.0	10.7	19.0	10.7
11-11.9	32.0	23.9	29.0	14.0
Per cent of patients less than 12 gm. per cent	63.5	39.2	55.1	28.3
12-12.9	23.0	30.9	29.0	35.3
13-13.9	10.0	25.0	13.0	32.0
14-14.9	3.0	4.3	1.7	3.1
15-15.9	0.6	0.63	0.7	1.0
16-16.9	0.06	0.03	0	0
17+	0	0	0	0.24
Total number of cases	7,835	3,520	170	1,274

ANEMIA OF PREGNANCY TREATED WITH MOLYBDENUM-IRON COMPLEX*

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REPORTS from our clinic in 1936 indicated that 11.5 per cent of our pregnant patients were anemic according to our standards for pregnancy; but if the standards for nonpregnant patients are used, then 63 per cent must be classed as anemic. Comparable figures for the 1947 group are 4.6 per cent with anemia of pregnancy and 39 per cent, using nonpregnant standards. The methods used are essentially the same, and we have studies in progress to determine the reason for the decrease in the number of anemic patients. In 1936, we stated that the control anemic patients showed as great an increase in hemoglobin formation during pregnancy as the anemic patients who received adequate amounts of ferrous or ferric salts. Our impression at that time was that iron salts were of comparatively little value in the treatment of anemia of pregnancy.

Talso and Dieckmann, in a recent report of 250 cases of pregnant patients with anemia, concluded that the administration of various iron preparations as well as various vitamin concentrates did not cause a significant increase in the rate of hemoglobin formation.

Healy, in 1946, stated that the administration of a molybdenum-iron complex seemed to be more efficacious in the treatment of nonpregnant anemia than iron alone.

Neary, also, in 1946, reported that molybdenum-iron complex resulted in an average gain in hemoglobin of 4.6 Gm. in 6.2 weeks as compared with 2.1 Gm. in 6.9 weeks for ferrous sulphate in pregnant anemic patients. There were only eleven patients in each group. He reported no failures with the special iron salt.

Initial and periodic hemoglobin determinations are very important parts of prenatal and postpartum care. The usual methods for determining hemoglobin—either with the visual or photoelectric colorimeter—require very small amounts of blood, 0.02 ml. and dilutions of 100 to 400 times. Thus the combined error of the pipette and chamber as well as the technician may be 7 per cent to 15 per cent. The hemoglobin concentration may fluctuate as much as 15 per cent (accurate method) and the hematocrit 7 per cent during a twelve-hour period. The hematocrit and erythrocyte count are methods for determining the number of red blood cells per unit of blood. The hematocrit has a closer correlation with the hemoglobin concentration than the red-cell count because the error in the former is approximately 2 per cent, while the minimum error in the red-cell count is over 8 per cent. For over ten years we have been using the hematocrit determination on heparinized blood as a screening method.

*The molybdenum-iron complex (Mol-iron) was supplied by the White Laboratories, Inc., Newark, N. J.

other iron salts so efficacious in pregnant patients. Our results with the molybdenum-iron complex have been so striking that; if the patient has taken this medication for three weeks and shown no significant increase in the hemoglobin concentration, the therapy is stopped and a more extensive study (bone marrow biopsy, gastric analysis, reticulocyte count, etc.) made to determine the cause of the anemia. Since the data was compiled we have had one other patient who showed a transient improvement during pregnancy but who also did not show an immediate increase post partum.

Fig. 1 shows the changes in hemoglobin, hematocrit, and erythrocyte count for the patients treated with molybdenum iron and a control group obtained simultaneously with the treated group as well as the control group reported by Talso and Dieckmann. The patients who were treated show a rapid increase in hemoglobin and hematocrit with a mean at term of 11.8 Gm. per 100 ml. and 36 volumes per cent—high figures for pregnant patients. The mean for the present control group is 10.7 Gm. of hemoglobin per 100 ml. and a hematocrit of 32.6 volumes per cent. The means for the Talso-Dieckmann control group are still lower. When these patients were again checked at six weeks post partum, the patients who had been on molybdenum iron had a mean of 12.2 Gm. per 100 ml. as compared with 11.2 for the present group and 11.5 for the Talso-Dieckmann group. Since the lower limit of the normal hemoglobin concentration in nonpregnant women is 12 Gm. per cent, many of our patients are still anemic at six weeks post partum. However, those who were treated had considerably higher hemoglobin levels than the controls. These studies indicate the need for a hematocrit determination at the six weeks post partum examination and for treatment if the patient is still anemic. We believe that the value of this molybdenum-iron complex has been demonstrated as being very effective in increasing the hemoglobin of pregnant patients who are anemic.

TABLE III. MEAN HEMOGLOBIN CONCENTRATION AT TERM AND SIX WEEKS POST PARTUM.
GM. PER 100 ML. OF BLOOD

	MICROCYTIC		
	NUMBER OF PATIENTS	TERM	SIX WEEKS POST PARTUM
Iron complex	49	11.6	12.2
Control	39	9.6	11.5
*Control	76	9.7	11.6
*Treated	174	10.9	12.0

*Talso-Dieckmann.

TABLE IV. R.D. 349096, AGED 24 YEARS

PRIMIPARA			GRAVIDA II PARA I		
DATE	HEMATOCRIT VOL. PER CENT	HEMOGLOBIN GM./100 ML.	DATE	HEMATOCRIT VOL. PER CENT	HEMOGLOBIN GM./100 ML.
9/17/45	40	13.3	11/13/47	36	12.0
12/27	34	11.3	12/ 8/47	33	10.8
3/ 4/46	31	9.8	1/ 8/48	33	10.6
		FeSO ₄ 1.0 Gm.			
3/28	31	9.0	2/ 5	34	
4/15	32	10.5	2/26	31	9.8
4/22	Delivery 3,265 Gm.		3/11	Mol-iron	
8/22	39	13.0	4/ 1	32	10.6
5/ 8/47	42	14.1	4/15	36	11.6
10/13	36	12.0	4/22		
			5/ 5	41	13.2
			5/ 5	Delivery 3,205 Gm.	
			5/12	41	14.2
			7/15	43	13.4

There were 49 patients in the treated group and 39 in the control group. Eight per cent of the treated group were normocytic, 10 per cent had a macrocytic anemia, and 81 per cent were microcytic. The control group were essentially the same. The nine patients comprising the normocytic and macrocytic groups all showed increases in hemoglobin, patients with the normocytic anemia showing the maximum increase. Two per cent of the patients with microcytic anemia showed a decrease even though they took adequate amounts of the iron complex. The erythrocytes of 28 per cent of the patients with microcytic anemia were hypochromic, 66 per cent were normochromic and 6 per cent were hyperchromic.

Heath, Murphy, and Fullerton have each stated that, if the hemoglobin is less than 8 Gm. per 100 ml., the hemoglobin concentration, if adequate iron therapy is administered, should increase 1 per cent or 0.16 Gm. per day. The maximum increase is reached between the second and fourth weeks. Below 8 Gm. and above 12 Gm. per cent in the nonpregnant patient the rate of increase is much less.

Forty-five patients gained an average of 2.11 Gm. hemoglobin before delivery; the minimum was 0.6 and the maximum was 5.5 Gm. Four patients showed no significant change. One could not take the medicine and another had a severe pyelitis which could not be treated (the patient was sensitive to all sulfonamide drugs and the causative bacillus had become resistant to streptomycin). We could not determine any cause for the persistent anemia in the other two patients, except the pregnancy. All four patients had low normal hemoglobin concentrations when examined two or more months after delivery. We do not believe that the anemia of pregnancy is due to the fetal demands for iron.

TABLE II. CHANGES IN HEMOGLOBIN CONCENTRATION IN THE TREATED GROUP

HEMOGLOBIN GM. PER 100 ML.	DURATION OF TREATMENT			
	2 WEEKS	3 TO 4 WEEKS	5 TO 6 WEEKS	6 WEEKS +
Decrease	2	1		
No change	0	1		
Increases				
0.1- .49	6	0		
0.5- .99	8	7	1	1
1.0-1.49	9	5	5	0
1.5-1.99	4	5	2	1
2.0-2.49	2	7	5	1
2.5-2.99	1	2	2	3
3.0-3.49		1	4	4
3.5-3.99			2	1
4.0+			2	
Mean increase-Gm.	1.1	1.73	2.36	2.7
Number of Patients	32	29	23	11

Table II illustrates the periods of treatment as well as the increases of hemoglobin for each period. Many of the patients appear in more than one period. Some patients showed the optimum increases for the period studied. The mean increases at two and four weeks, however, do not amount to 1 per cent per day but are approximately 0.08 Gm. per day. The increase at six weeks, however, is not quite as great as one would expect, but it must be remembered that by this time many of the pregnant patients had hemoglobin concentrations that were within the normal range for pregnancy and obviously would not show the expected increase. The most outstanding finding is that after two weeks only two out of 32 patients showed a further decrease and at four weeks only one showed a decrease and one no change. We have never had

Table IV contains data from two pregnancies in R.D., number 349096, a 24-year-old private patient of the senior author. This woman is intelligent and very cooperative. Extensive studies of her diet and protein balance were made in her second pregnancy. The average protein intake was 78.4 Gm. per day (1.61 Gm. per kilo), and the average food iron intake was 10.9 Mg. per day. The months of the year and the hemoglobin levels for the two pregnancies are exactly the same. In a six-week period in the 1946 pregnancy, while taking 1 Gm. of ferrous sulphate daily, the hematocrit increased from 31 to 32 and the hemoglobin from 9.8 to 10.5. In the 1948 pregnancy in a five-week period, the hematocrit increased from 31 to 36 and the hemoglobin from 9.8 to 11.6 and three weeks later at term the hematocrit was 41 and the hemoglobin 13.2 Gm. per cent.

Discussion

The increases in hemoglobin were so dramatic and so rapid that we postulated a possible decrease in plasma volume. A few studies, however, have indicated that there was no decrease in the plasma volume and the consistent and sustained increase in hemoglobin extending into months after delivery indicate even better than blood volume determinations that there was an actual increase in the amount of hemoglobin.

There were no alterations in the patients' diets to which the increases in hemoglobin might be attributed. So far as we can tell the control and treated groups are identical. Only one patient stated that she had to decrease the amount because of the gastrointestinal discomfort.

Summary

The hematocrit determination is an easy, rapid, and accurate method of determining which patients have anemia. It is more accurate than the hemoglobin concentration as it is usually determined. Pregnant patients should have a hematocrit determination every three months, one at or near term, and one also at six weeks post partum. A hemoglobin which is less than 12 Gm. (hematocrit 37 per cent) in the first twelve weeks or which is not 12 Gm. or more six weeks post partum is indicative of anemia. From the twelfth to the thirty-sixth week the lower limit of the hemoglobin in pregnancy is 10 Gm. (hematocrit 30 per cent) per 100 ml. The lower limit from 36 weeks to term is 10.5 Gm. (hematocrit 32 per cent) per cent.

A molybdenum-iron complex has been found to be very effective in causing significant increases in the hemoglobin concentration of most patients with anemia of pregnancy within a three-week period. If the hemoglobin does not show a significant increase in this period of time, further hematologic studies are indicated.

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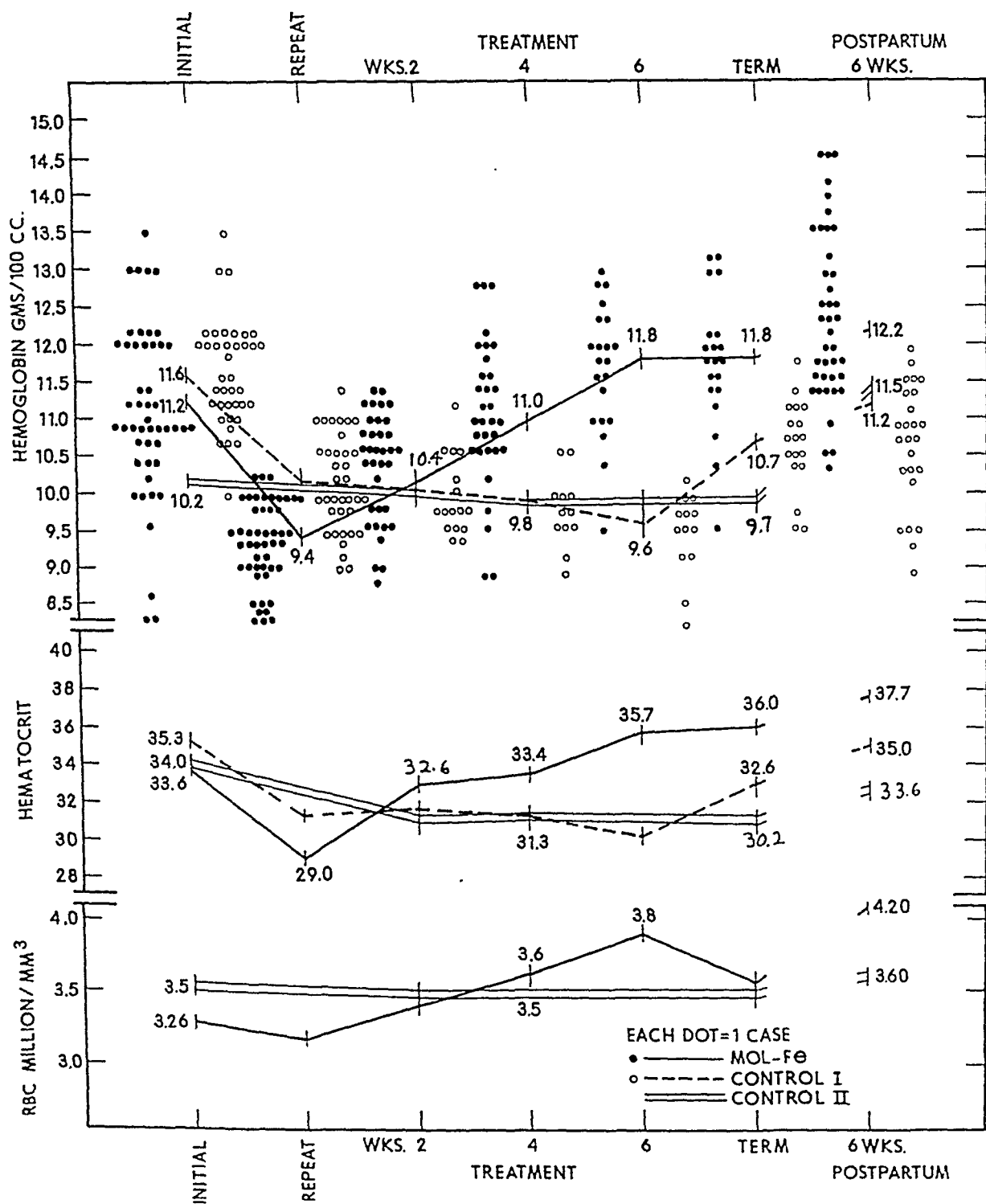


Fig. 1.—Therapy was started after the repeat determination in the treated group. Solid dot indicates treated case and circle is a control. Control curve I is untreated anemic patients followed in present study. Control curve II is taken from Talso-Dieckmann study based on patients studied between 1936 and 1945.

were recorded during these respective critical periods. The fact that 41 out of 42 recurrent endometrial cancers were observed within five years of treatment confirms the practical safety of considering as probably cured patients who survive this period without evidence of recurrence. The average interval of recurrence in the 41 cases was 18.6 months, as compared with 14.5 months for patients with cervical cancer.

The type of treatment which was received by these uncured patients is shown in Table II, with the average recurrence interval for each type of treatment. With the exception of one case in which subtotal hysterectomy was performed, hysterectomy signifies removal of the entire uterus with both tubes and ovaries. The average dose of intrauterine radium, in the cases for which it was used, was 3,344 mg. hr. X-ray therapy, when employed, was usually given as a course of 16 to 20 treatments of 300 r. each through 4 pelvic ports, with the 200 kv. machine and protective filters of copper and aluminum. Although only six patients were treated with preoperative radium followed by hysterectomy, it is interesting that their average time of recurrence was only 12 months, as compared with 24 months in a larger group of patients who were treated by hysterectomy alone. This comparison indicates no advantage for preoperative radium, a conclusion which was also reached by another approach in a recent study of all the surgically treated cases of corpus cancer at the Roosevelt Hospital.

TABLE II. AVERAGE RECURRENCE INTERVAL OF ENDOMETRIAL CARCINOMA ACCORDING TO TYPE OF TREATMENT

TREATMENT	CASES	PER CENT	INTERVAL (MONTHS)
Hysterectomy	17	41	24
Radium	11	27	18
Radium and hysterectomy	6	15	12
Radium and X-ray	4	10	11
Hysterectomy and X-ray	2	5	11
Radium, hysterectomy and X-ray	1	2	22
Total	41	100	18.6

The average recurrence interval in relation to the clinical stage of the tumor at the time of original treatment is shown in Table III. It is well known that patients with early lesions have the best prognosis in terms of five-year cure rates. Table III suggests a better prognosis for patients with early tumors, even though uncured, in that they had a longer average interval between treatment and recurrence than did patients with more advanced lesions. Table IV in a similar manner indicates a longer average period of freedom from recurrence in patients with tumors of low than of high histologic grade, just as the cure rate is higher for the former also. Healy and Brown (1939) have demonstrated the best prognosis in endometrial carcinoma, as evidenced by five-year survivals, to be associated with well differentiated tumors; that is, those of low histologic grade. This observation was confirmed in a recent study of the cases treated at the Roosevelt Hospital.

TABLE III. AVERAGE RECURRENCE INTERVAL OF ENDOMETRIAL CARCINOMA ACCORDING TO CLINICAL STAGE

STAGE	CASES	PER CENT	INTERVAL (MONTHS)
Early	7	19	30
Intermediate	10	27	12
Advanced	20	54	16
Total	37	100	

THE TIME OF RECURRENCE OF ENDOMETRIAL CARCINOMA

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MALIGNANT tumors differ from one another in their characteristic rate of growth. Some, such as basal-cell carcinomas of the skin, are typically slow in their development and spread; while others, like malignant melanomas, are notoriously rapid in their dissemination through the body and their usually fatal termination. Tumors of the uterus occupy an intermediate position in this respect. The time of recurrence of a series of epidermoid carcinomas of the cervix after radiation therapy has been reported in another study. The present paper presents data concerning the rate of growth of adenocarcinoma of the endometrium.

Information bearing on this problem has been obtained from a study of three groups of cases. The first group comprises patients who presented clinical evidence of tumor recurrence at varying intervals following treatment for carcinoma of the endometrium. Group 2 consists of patients in whom corpus cancer was recognized after the administration of intrauterine radium for presumably benign lesions but whose original curettings on restudy showed carcinoma to have been present. Group 3 includes patients in whom the diagnosis of endometrial carcinoma was missed at the initial curettage and who received no other treatment until the later discovery of the tumor.

GROUP 1.—The gynecologic files of the Roosevelt Hospital contain records of 42 treated cases of carcinoma of the endometrium in which the time of recurrence of the tumor was noted in the history. Forty-one of the recurrences occurred within 5 years of treatment. These cases are summarized in Tables I to IV. The unincorporated case is reported in detail because of its unusual interest.

TABLE I. INTERVAL BETWEEN TREATMENT AND RECURRENCE OF CARCINOMA OF ENDOMETRIUM

INTERVAL (MONTHS)	CASES	PER CENT
0-6	8	20
7-12	12	29
13-24	11	27
25-36	5	12
37-48	3	7
49-60	2	5
Total	41	100
Average interval		18.6 months

The distribution of the cases according to time of recurrence is presented in Table I. Practically half (49 per cent) of the recurrences were noted within the first year, and three-fourths (76 per cent) within the first two years. In a similar study of cervical cancer, 57 per cent and 84 per cent of the recurrences

CASE 3.—E. L. (R. H. No. 13953, No. 15343, and No. 18303), a white spinster of 57 years, was admitted for curettage on Nov. 7, 1925, because of recent postmenopausal bleeding. Her periods had ceased at the age of 53 years. Although the curettings were diagnosed as hyperplasia of the endometrium, restudy several years later (Taylor, 1932) led to a change in diagnosis to adenocarcinoma, Grade 1. The patient was treated with 600 mg. hr. of intrauterine radium. When she returned on May 20, 1927, with a recurrence of the bleeding, another curettage was performed, but the diagnostic error was repeated and intracavitary radium was reapplied for only 900 mg. hr. After freedom from symptoms for three years the patient returned on June 24, 1930, bleeding again. Operation this time consisted of hysterectomy and bilateral salpingo-oophorectomy. The entire endometrium was invaded by a diffuse, well-differentiated adenocarcinoma with the same histologic characteristics as the tumor in the original curettings. There was minimal involvement of the myometrium.

Comment.—The extent to which the progress of the lesion was retarded by the two scrapings of the endometrial cavity and the 2 small applications of radium is uncertain. It is interesting, however, that the tumor remained in an early clinical stage for almost five years.

CASE 4.—A. P. (R. H. No. 36210), a 54-year-old white woman with three children, had a curettage at another hospital on Jan. 13, 1944, because of menometrorrhagia. Although the curettings showed atypical glandular hyperplasia and an area of adenocarcinoma, the only treatment given the patient was 2,200 mg. hr. of intrauterine radium. Her bleeding stopped, only to recur two years later, three weeks before admission to the Roosevelt Hospital on Feb. 4, 1946. The curettings obtained at this time were diagnosed as adenocarcinoma, Grade I. When the uterus was removed, sections showed only slight invasion of the muscle wall, but metastatic tumor was present in the right ovary.

Comment.—The growth of this tumor over a two-year period was interrupted only by a curettage and inadequate irradiation. Although histologic section of the fundus indicated only slight invasion of the myometrium by carcinoma, metastatic tumor had taken hold already beyond the limits of the uterus.

In each of the three cases in this group, growth of the endometrial cancer continued at a sufficient rate, following intrauterine irradiation, to cause a recurrence of symptoms and thereby to make its presence known within five years. Although in Case 2 the tumor was still in an early clinical stage after four years eight months, in Case 3 ovarian metastasis occurred within two years. Scheffey (1942) has suggested that intracavitary radium, as used to control bleeding of benign origin, may actually retard malignant growth. Two of his patients with corpus cancer had been treated seven and twelve and one-half years previously with 2,400 mg. hr. and 1,200 mg. hr. of intrauterine radium, respectively. Review of the original curettings, which had been interpreted as benign lesions, led to a revision of the diagnosis to carcinoma in each case. Whether the secondary tumors were recurrences or new growths must remain an open question. There is suggestive evidence that radiant energy itself may be carcinogenic for the endometrium.

GROUP 3. This group comprises three cases in which carcinoma of the endometrium was present but was not diagnosed at the time of initial curettage. The patients received no further treatment until the carcinoma became clinically evident at later dates. In one case, in which two and one-half years had elapsed, the lesion, a Grade I adenocarcinoma, was still in a clinically early stage, being confined to the endometrium. In the second case, the tumor, a Grade II papillary adenocarcinoma, was discovered three years after the initial curettage. During the interim it had metastasized to one ovary and the omentum. The third case is reported in detail because of its unusually slow growth.

CASE 5.—M. T. (R. H. No. 4352 and No. 18610), an unmarried white woman of 45 years of age, had a curettage on June 15, 1914, because of metrorrhagia. The following is an excerpt from the pathologic report:

TABLE IV. AVERAGE RECURRENCE INTERVAL OF ENDOMETRIAL CARCINOMA ACCORDING TO HISTOLOGIC GRADE

GRADE	CASES	PER CENT	INTERVAL (MONTHS)
1	11	42	21
2	10	38	16
3	5	19	13
Total	26	99	

In summary, our records show that out of 42 patients with endometrial carcinoma in whom viable tumor cells remained after definitive treatment, regrowth of the residual tumor to a clinically apparent stage occurred in 41 within five years; and in three-fourths of these patients the recurrence was evident within two years. The single case of later recurrence is described below.

CASE 1.—K. H. (R. H. No. 41882), a 56-year-old white private patient of Dr. William P. Healy, had a curettage at another hospital on Nov. 8, 1938, because of postmenopausal bleeding of 5 months' duration. Her last menstrual period had been 6 years previously, at age 50. A sister had died at age 74 with breast cancer. Pathologic report on the curettings was "papillary adenoma malignum" (adenocarcinoma, Grade I) (Fig. 1). The patient was treated with 3,600 mg. hr. of intrauterine radium in corpus tandem. When examined ten months later, she felt well and there was no evidence of neoplastic disease. She remained well and bled no more until eleven days before her admission to the Roosevelt Hospital eight years later, on Jan. 20, 1947, at the age of 64 years. Recent endometrial biopsy was said to have shown adenocarcinoma. The day after admission total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed. The uterus was enlarged to twice normal size and was filled with a yellowish tumor mass which had invaded the myometrium deeply but had not yet penetrated the serosa. Histologic section showed an undifferentiated carcinoma of the endometrium, Grade III. (Fig. 2.)

Comment.—This case is interesting because of the long latent period (over eight years) between initial treatment and symptoms of recurrence. The histologic difference between the two tumor specimens suggests the possibility that the second tumor was an independent neoplasm rather than a recurrence of the original one. Although distinctly unusual, such late recurrences of fundal carcinoma are not unheard of. Barrows (1944) reported a case with recurrence nine years after radium therapy; and Suitor (1947) has recently reported a pelvic recurrence eleven years later in a patient who had a total hysterectomy (without removal of the adnexa) and postoperative x-ray treatment for corpus cancer.

GROUP 2.—In this group were three patients who received inadequate intrauterine irradiation for endometrial cancer in the mistaken belief that the lesion was benign. With the return of symptoms the carcinoma was discovered two to five years later.

CASE 2.—V. A. (R. H. No. 14028 and No. 15881), a 72-year-old white woman with three children, was admitted for curettage on Dec. 14, 1925, because of a bloody vaginal discharge which she had had for four weeks. Spontaneous menopause had occurred at age 40. Pathologic report on the curettings was endometrial hyperplasia and the patient was treated with 500 mg. hr. of intrauterine radium. Additional sections of the same curettings were cut several years later by Dr. H. C. Taylor, Jr. (1932), who discovered a region of papillary adenocarcinoma, Grade I. The patient was asymptomatic for two years after treatment, when she returned (Nov. 4, 1927) with a recurrent bloody discharge. Curettage at this time revealed Grade I adenocarcinoma. Accordingly, total hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was normal in size and contained two small papillary tumors of the endometrium with no demonstrable invasion of the myometrium.

Comment.—This tumor, of low-grade malignancy, underwent little growth over a period of two years. Progress of the tumor was probably impeded to some extent by the small dose of radium which the patient received.

contained a large polypoid growth which protruded through the external os. Biopsy of this tumor on Oct. 20, 1930, showed an adenocarcinoma, Grade II.

Comment.—Although impossible of proof, the fact that the patient continued to bleed intermittently between her two hospital admissions strongly suggests her having harbored the same uterine tumor for over sixteen years. So slow a rate of growth is extraordinary for untreated endometrial cancer, and this is perhaps the longest history of its kind on record. Taylor's paper of 1932 included two other cases of carcinoma of the endometrium with histories of possibly fourteen and fifteen years, but the early existence of these tumors is questionable since curettage had not been performed.³

Discussion

The time required for the clinical recognition of a tumor's recurrence is the resultant of several factors. Among these are the diligence and diagnostic aids used in the search for the tumor, the vital organs encountered by it in the course of its spread, and its rate of growth. There is little, if any, evidence for a fundamental difference in actual rate of growth between uterine tumors of cervical and those of endometrial origin. They grow at an accelerated tempo during the stages in which they are clinically recognizable. Although rare instances of recurrence after periods of over fifteen years have been noted for both types, the overwhelming majority of unsuccessfully treated ones become manifest within five years and usually within two years. In their incipiency, on the other hand, both cervical and endometrial lesions may advance quite slowly. Taylor and Guyer (1946) have recently reported a seven-year history in a case of early cervical cancer. In two recent cases at the Roosevelt Hospital, almost six years elapsed between the recognition of an atypical hyperplastic change in the endometrium and its development into a clinically and pathologically early malignancy.

Summary

1. In 41 out of 42 unsuccessfully treated cases of endometrial carcinoma, recurrence of the tumor was observed within five years. Half of the recurrences were noted within the first year of treatment and three-fourths within the first two years.

2. Two unusual cases of corpus cancer are reported, with histories of eight and sixteen years.

3. Preoperative radium irradiation of the uterus in surgically treated cases neither improved the five-year cure rate nor prolonged the interval of tumor recurrence.

4. Tumors in an early clinical stage of development when treated recurred later than did those in more advanced stages.

5. Tumors of low histologic grade recurred later than the less differentiated ones.

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“The tissue consists of a papillomatous overgrowth of the endometrium which is made up of closely placed, dilated, and tortuous acini, the individual cells of which are quite regular. Very little stroma can be seen, there being just enough to act as a superstructure for the epithelium. There is no positive evidence of malignancy but this type of growth possibly may become so.”

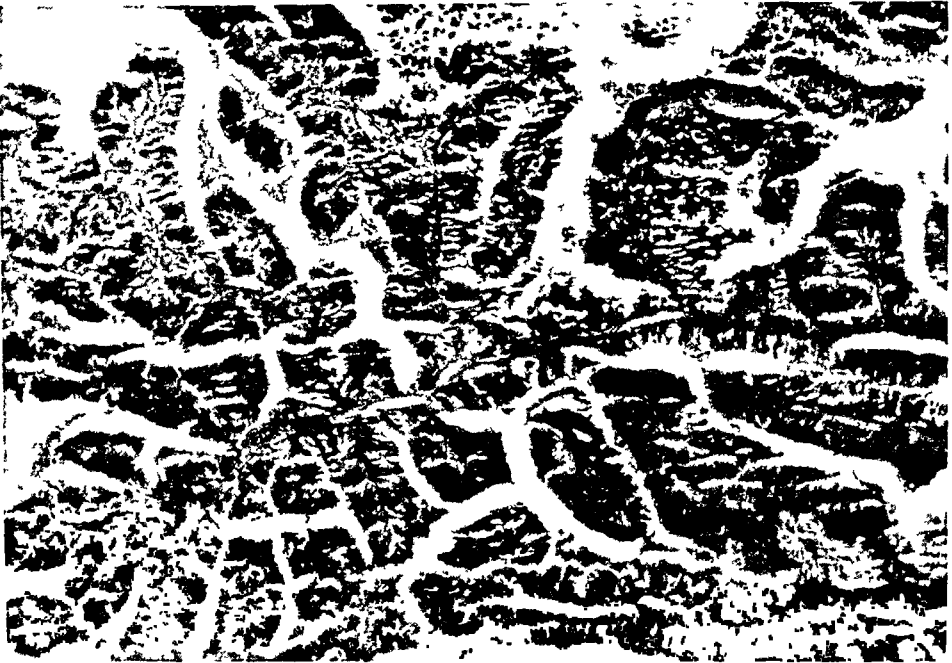


Fig. 1 (Case 1).—Curettings showing adenocarcinoma of endometrium, Grade I.

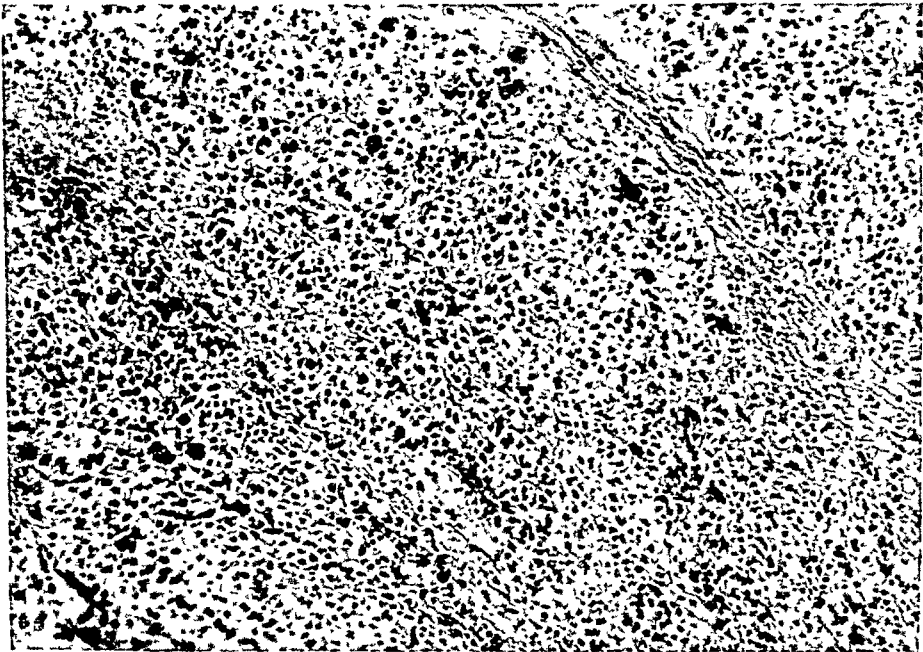


Fig. 2.—Same case, eight years later. Adenocarcinoma of endometrium, Grade III.

The section was reviewed later by Dr. H. C. Taylor, Jr. (1932) who diagnosed the lesion as a typical Grade I adenocarcinoma. Although the history is lacking in detail, the patient apparently flowed off and on from 1914 to 1930, when she was readmitted to the hospital, at age 61, sixteen years after the original curettage. The uterus was small but

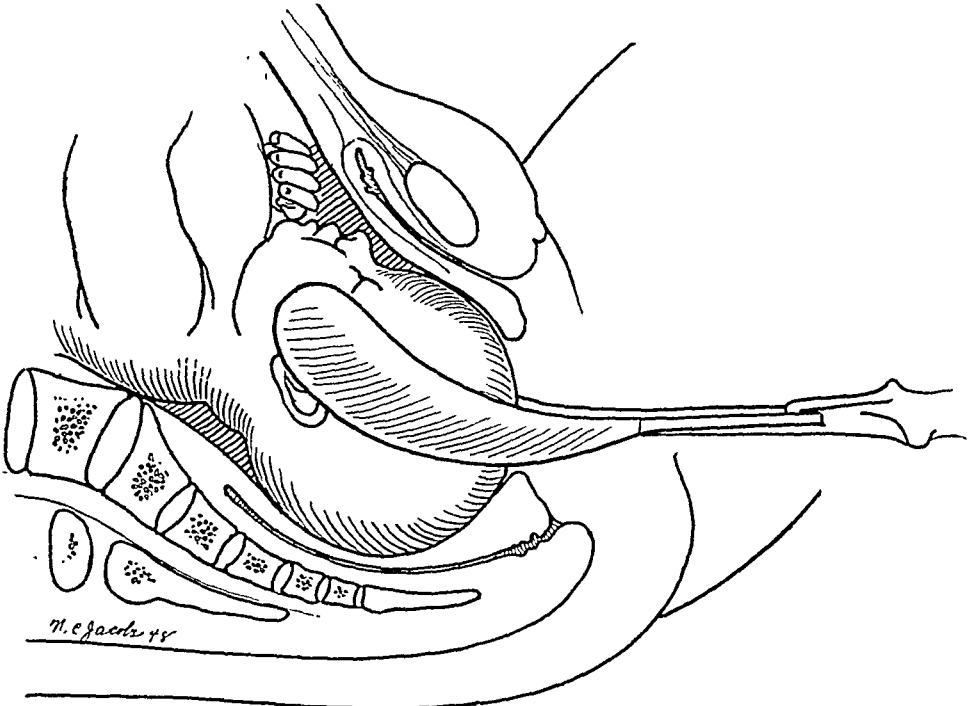


Fig. 1.—Original application of forceps for the posterior position.

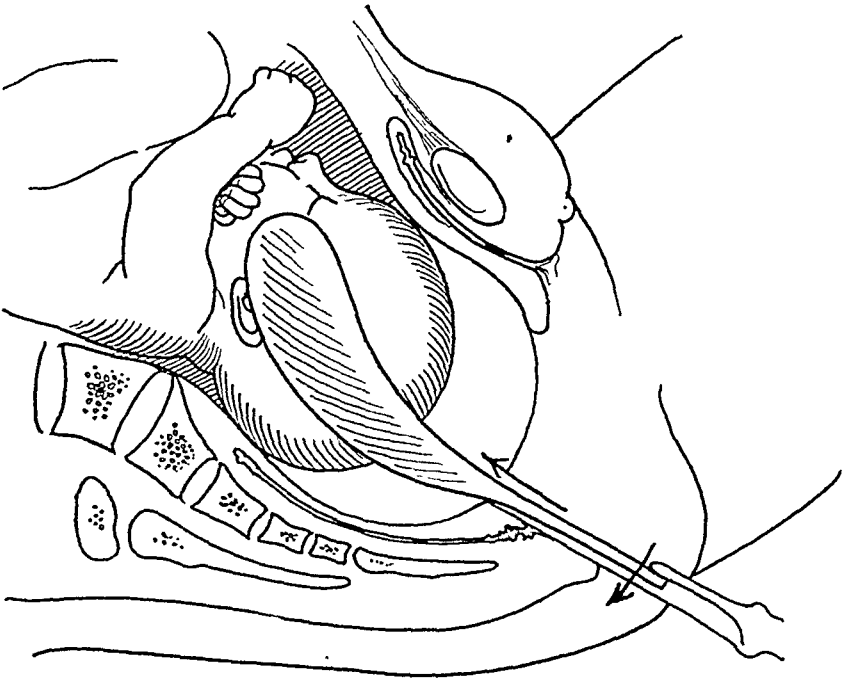


Fig. 2.—Downward and backward depression of the forceps handles with upward dislodgment of the head.

A METHOD OF FORCEPS ROTATION IN POSTERIOR POSITIONS

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THE Scanzoni maneuver, the Bill modification of the Scanzoni operation, and manual rotation of the head have been the most widely applied methods of rotation of the head in persistent posterior positions. Occasionally, it is feasible to extract the head by forceps without rotation.

To the uninitiated, rotation with forceps by the Scanzoni method is not without the danger of damage to the maternal soft parts because of the tightness of these parts at the plane at which the rotation is done. In rotation done manually, the head is usually dislodged, and, although it occurs infrequently, prolapse of the cord is a constant threat. Also, with manual rotation of the head, not infrequently the head cannot be sufficiently fixed to prevent conversion to the original posterior position before, or when, the forceps blades are applied. However, the danger of soft tissue damage, when manual rotation is done, is minimal. Since there is so little trauma with manual rotation, the method of forceps rotation of the posteriorly placed head by upward dislodgment prior to rotation was conceived.

Nonfenestrated blades of the Tucker-McLean type with long shaft and with the cephalic portion extending from the shaft at about a 30-degree angle are used, since the head is usually incompletely flexed in the posterior position. The station of the head above or below the spines, or on the pelvic floor, does not preclude the use of this method. All the tenets pertaining to the use of forceps must be followed, i.e., complete dilatation of the cervix, or as complete dilatation as can be obtained with posterior positions, ruptured membranes, an adequate cephalopelvic relationship, and an empty bladder. In addition, though not an absolute necessity, a level of anesthesia should be used that will give proper degree of relaxation of the uterus but not to the degree required for version and extraction. This method of rotation has been done under gas-oxygen-ether, cyclopropane, spinal, caudal, and Delvinal supplemented with gas-oxygen anesthesia.

It is best that the patient's buttocks should hang over the edge of the delivery table slightly. The reason for this precaution will be self-evident.

After the position has been accurately determined, the first application of forceps is made, exactly as in the Scanzoni maneuver, i.e., if the position is found to be right occipitoposterior, the Tucker-McLean forceps are applied for a left occipitoanterior position, with the pelvic curve of the forceps directed toward the baby's face, if occipitoposterior for occipitoanterior, etc. (Fig. 1.) It is absolutely essential that the forceps be closely applied to the head and be inside the cervix, when complete retraction of the cervix has not been effected. The handles of the forceps should lock easily and accurately. The handles of the forceps are then pushed back toward the table at about a 45-degree angle with the floor. As this is done, the shaft is pushed gently upward into the pelvis. At this point, the shaft pushes against the perineal body. As the upward thrust is begun and the head is dislodged above the spines, the handles of the forceps are rotated on their axis, clockwise in a right occipitoposterior position, counter-clockwise in a left occipitoposterior position (Fig. 2 and Fig. 3). The backward push, upward thrust of the shaft, and rotation of the blades are actually one gentle, coordinated movement. Minimal exertion of force is necessary. In performing this procedure, the head is swung around in the wide arc, whereas the

handles of the forceps rotate on their axis in a small arc; the opposite of the procedure used in the Scanzoni operation. Frequently, the head completes the rotation with extremely little tension, once the rotation is gently started.

When rotation from occipitoposterior is desired and the original position is not known, an exploratory gentle effort at rotation to the right or left may be attempted. Almost invariably the head will rotate to the original position, right occipitoposterior or left occipitoposterior, with greater ease than to the opposite position.

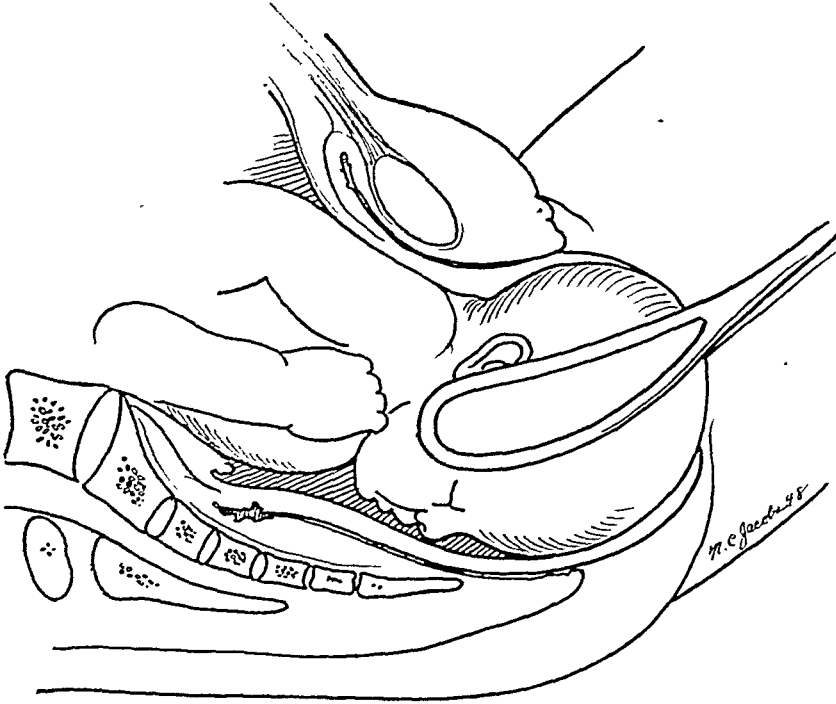


Fig. 5.—Second pair of forceps applied.

When the head has been completely rotated to occipitoanterior position through the 135 to 180 degree arc, it is pulled well down into the pelvis (Fig. 4). While pressure is exerted on the fundus, the inverted blade that is to be replaced in the anterior position is removed first, i.e., if the original position had been left occipitoposterior, the blade to be removed from the left side of baby's head and mother's pelvis will be replaced first. The second blade is removed after the first blade has been replaced. The McLean-Tucker forceps have been replaced by DeWees, Elliotts, Simpsons, or Tarniers in the second application. The remainder of the forceps delivery is completed in the usual manner (Fig. 5).

The time of doing the episiotomy is optional. We have found it more desirable to do the episiotomy, usually of the mediolateral type, after the rotation has been completed and the forceps reapplied. We feel that extension of the episiotomy into the vaginal sulci is less apt to occur if the episiotomy is done late.

The method has many advantages: 1. there is little trauma to the vaginal mucosa and its underlying fascia since the head has been rotated high in the pelvis or at the pelvic brim; 2. the rotation is well controlled, more so than by manual rotation; 3. in the case of prolapse of the cord, which we have seen very rarely, there is little danger to the baby, since the delivery is usually completed within a few minutes after rotation has been completed.

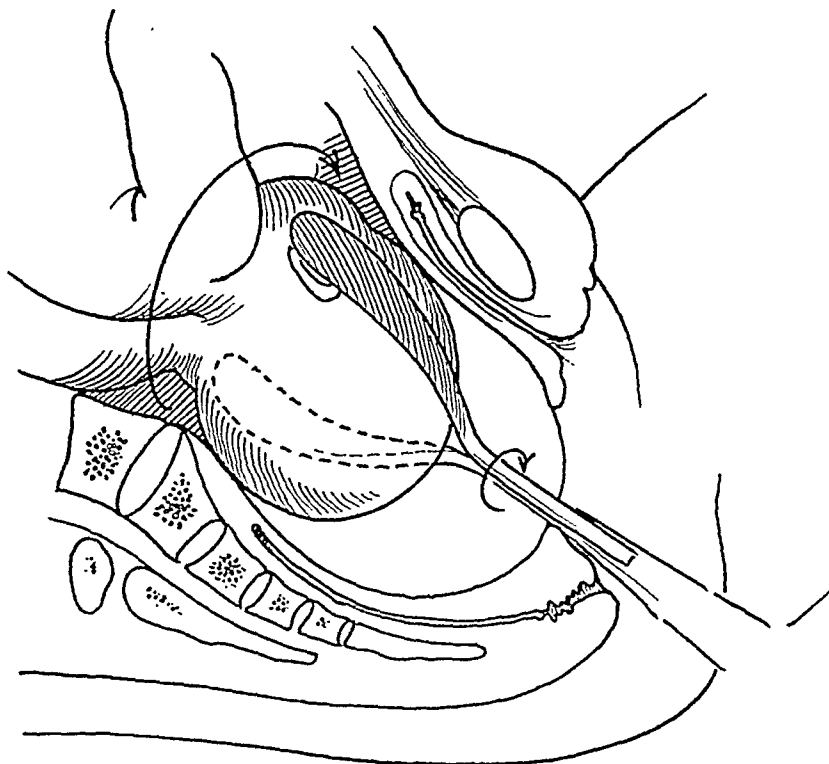


Fig. 3.—Rotation of the head. Note.—b and c, though represented separately, are one coordinated movement.

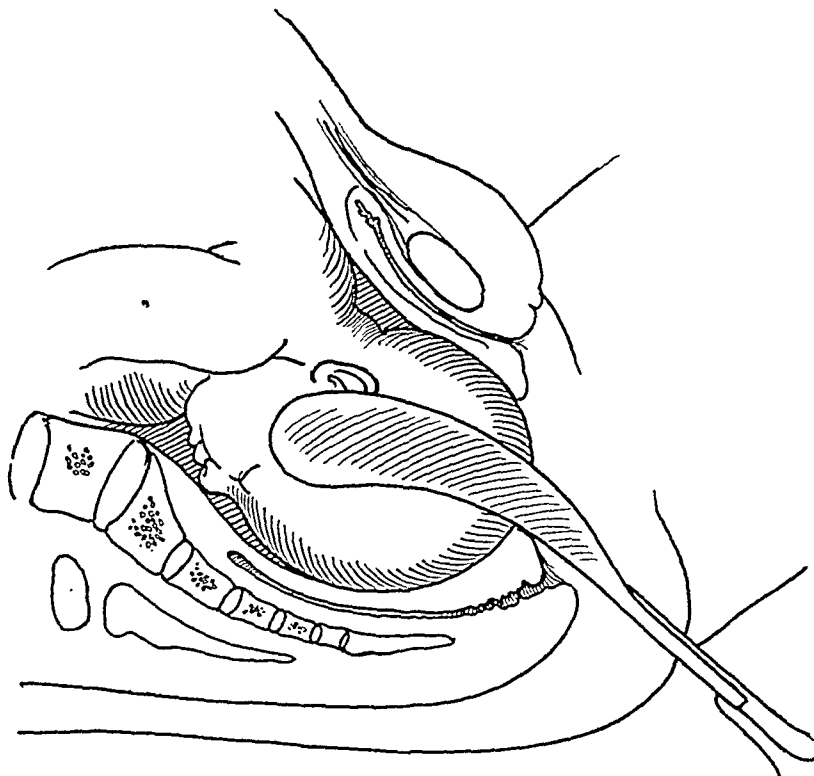


Fig. 4.—Head has been pulled deep into pelvis with forceps inverted.

condition. Approximately three months later she visited her family physician because of vaginal bleeding following intercourse, and an inverted uterus was found. Upon readmission to the hospital on June 3, 1931, her general condition was excellent and the blood count normal. Two days after admission, the uterus was replaced manually under gas-oxygen anesthesia. The cervix was so soft and patulous that three interrupted sutures were placed

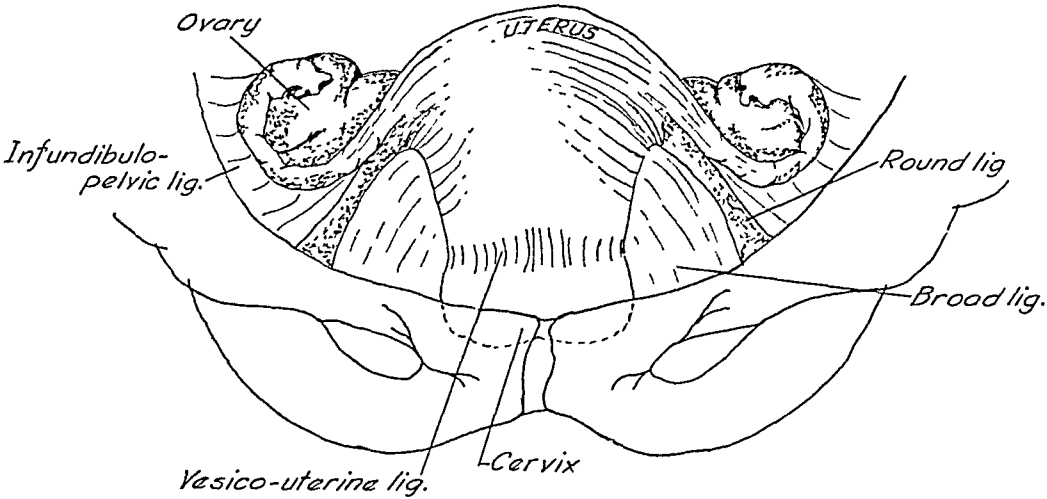


Fig. 1.

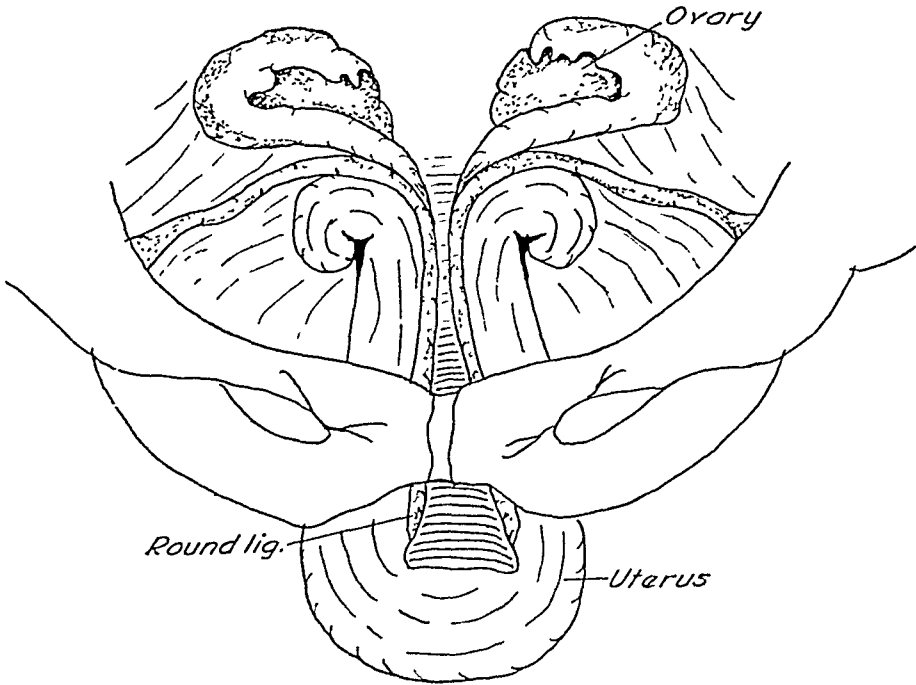


Fig. 2.

through the lips of the cervix with the idea of preventing a recurrence. The patient made an uneventful recovery without fever or symptoms, and was discharged eight days after reposition of the uterus. Two months later examination by her physician revealed the uterus in good position and condition. In 1937 an operation was performed for salpingitis, and the uterus was found to be in good position.

A NEW CONCEPT IN THE REPLACEMENT OF THE INVERTED UTERUS AND A REPORT OF NINE CASES*

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IT IS the purpose of this paper to describe the method used in replacing the inverted uterus to its normal position, and to report nine such cases. This method of replacement was successful in all.

Several operations have been devised to correct the inverted uterus. The method to be described does not require any surgical procedure, and may be called "manual replacement." The uterus cannot be replaced by dimpling or making pressure on the fundus uteri or by any procedure in which the uterus is allowed to remain in the pelvis. The uterus must be lifted into the abdominal cavity above the level of the umbilicus, at which time the passive action of the uterine ligaments corrects the malposition. The entire procedure depends upon this action of the uterine ligaments. Therefore attention is called (Fig. 1) to the origin and insertion of these ligaments; namely, the round, broad, uterosacral, and uterovesical. Fig. 2 shows the ligaments as they appear in an inverted uterus when the uterus is in the pelvis. The ligaments are not altered in tension or length by the inversion of the uterus per se. To replace the inverted uterus the entire hand is placed in the vagina with the tips of the fingers at the uterocervical junction and the fundus uteri in the palm of the hand. The entire uterus is then lifted out of the pelvis and forcefully held in the abdominal cavity above the level of the umbilicus. It is shown in Fig. 3 that all the uterine ligaments are stretched and very tense because the distance between the origin and insertion of the ligaments is greatly increased by this maneuver. This is in contrast to the relaxed and unaltered condition of the ligaments when the inverted uterus is in the pelvis. The ligaments are so situated that, when they are placed under tension, pressure is exerted first to widen the cervical ring, second to pull the fundus through it, and thereby replace the uterus to the normal position. It is necessary to hold the uterus in this position for a period of three to five minutes, at which time the fundus recedes from the palm of the hand, as shown in Fig. 4. It is emphasized that in order to accomplish this procedure the entire hand and two-thirds of the length of the forearm must be placed in the vagina, otherwise the pull and tension of the ligaments are not sufficient to correct the condition.

CASE 1.—G. K. (St. Joseph Hospital), a white multipara, para ii, gravida iv, aged 26 years, was admitted on Mar. 12, 1931. The antepartum course and previous history were uneventful. A spontaneous delivery of a living female child in the occiput posterior position occurred at 4:28 A.M. on March 12. The placenta was delivered intact twenty minutes later followed by a profuse hemorrhage. Morphine, $\frac{1}{4}$ grain, oxytocics, 1,000 c.c. of saline, and 600 c.c. of blood were administered. She was discharged on the sixteenth day in good

*Presented at a meeting of the Brooklyn Obstetrical Society, March 5, 1948.

CASE 3.—D. T. (St. Joseph Hospital), a white multipara, para i, gravida ii, aged 30 years, was admitted in active labor at 12:30 P.M., Feb. 2, 1939. Her previous pregnancy and history were uneventful. She had been in labor for about an hour and a half before admission. After an episiotomy was performed, the spontaneous delivery of a living male child occurred at 1:20 P.M. Under ether anesthesia the episiotomy was repaired. Several attempts were made to express the placenta. There was practically no vaginal bleeding. Twenty minutes after delivery more than the usual amount of pressure was exerted upon the fundus. The

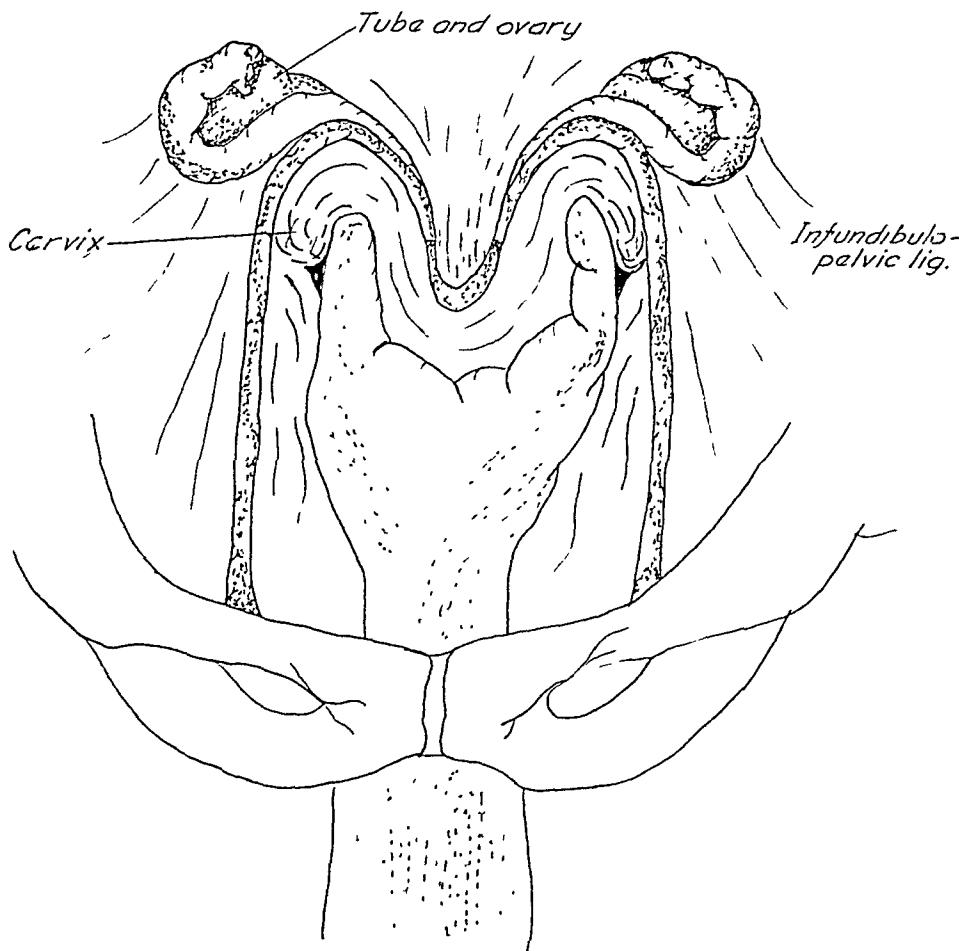


Fig. 4.

placenta appeared at the introitus in the manner of an inverted umbrella. It did not separate and was removed manually. During the removal, the placenta was found to be adherent to an inverted uterus. I was unable to determine whether or not the placenta was attached at the fundus; however, it appeared to be. During this time the patient was coming out of the ether anesthesia. There was no evidence of shock, and bleeding was about 100 c.c. She was immediately anesthetized with ether, and the uterus was repositioned. The vagina was packed with iodoform gauze. Her condition was good, blood pressure 80/50, pulse 126. The vaginal packing was removed five hours later, and the postpartum course was uneventful. She was discharged on the tenth day in good condition; vaginal examination revealed no abnormalities. Six weeks post partum, the uterus was in good position and condition. This patient was delivered again on Jan. 30, 1948, uneventfully.

CASE 4.—H. R. (South Nassau Communities Hospital), a white primipara, aged 25 years, with an uneventful previous history, was admitted April 7, 1939. After a fourteen-hour labor

CASE 2.—G. K. (Rockaway Beach Hospital), a white primipara, aged 19 years, was admitted June 20, 1936. Previous history and prenatal history were uneventful. After about fourteen hours of labor at 4:30 P.M., the patient was delivered of a living female child by means of low forceps. A second degree laceration was repaired. After many attempts and an excessive amount of Credé, the placenta and membranes appeared at the vagina thirty-one minutes after delivery. The placenta was removed from the vagina with much difficulty, followed by profuse bleeding for which the vagina was packed. The patient was placed in Trendelenburg position, given 500 c.c. of glucose intravenously, morphine, and oxytocics.

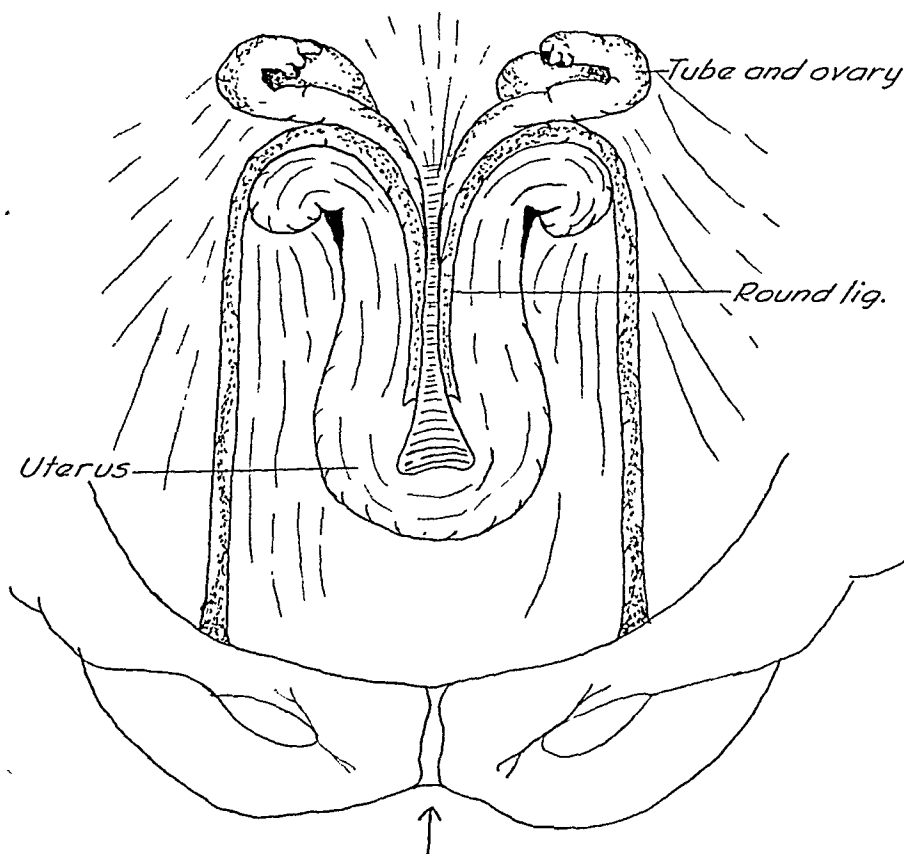


Fig. 3.

Bleeding continued in spite of packing. I saw this patient at 4:30 A.M., on June 21, approximately eleven hours after delivery. She was in severe shock, pulse 150, blood pressure 40 and at 5:30 A.M., 500 c.c. of blood were given. At 5:40 A.M. the vaginal packing was removed and an inversion of the uterus was revealed. Under gas oxygen anesthesia an attempt was made to reduce it. This was unsuccessful, and the vagina was packed with mercuriochrome soaked gauze. For the next ten days the patient's condition was not good: vaginal bleeding moderate, red blood count 1,920,000, hemoglobin 34 per cent, temperature ranged from 100 to 104° F., marked abdominal distention, severe abdominal cramps, and catheterization was necessary. During this period two more transfusions were given, totaling 1,210 c.c. From the tenth to the fourteenth day her general condition improved and the temperature was normal. On the fourteenth day post partum under gas oxygen anesthesia the uterus was replaced. A suture was also placed through the cervical lips in this case. For the next week the patient had a temperature ranging from 103° F. to normal, after which time it remained normal. On the twenty-fifth day post partum, the blood count was normal, and upon vaginal examination there were no abnormal findings. On August 18, six weeks post partum, vaginal examination was negative except for an eroded cervix which was treated by cauterization. She has since been delivered of a baby with no difficulties during the third stage of labor.

CASE 8.—I. F. (South Nassau Communities Hospital), a white primipara, aged 28 years, was admitted April 17, 1945. She was delivered at 9:46 A.M. by low forceps after ten hours of labor. At 10:10 A.M. the placenta was delivered intact with a moderate amount of bleeding. At 11:40 A.M. profuse bleeding occurred, the pulse and blood pressure were not obtainable, and plasma was administered. This patient was seen for the first time at 12:15 P.M. by my associate, Dr. George E. Christmann. Vaginal examination revealed an inverted uterus which was replaced and packed under gas-oxygen anesthesia. During this time the patient had received four pints of plasma, and at 3:00 P.M. a pint of blood. The following morning her condition was much improved, the uterine packing was removed, and another pint of blood was given. The patient had a temperature of 101° to 102° F. for four days, and was discharged on the twelfth day post partum in good condition.

CASE 9.—M. G. (St. Joseph Hospital) a white primipara, aged 29 years, was admitted June 20, 1947, and was delivered by low forceps at 4:28 P.M. after twelve hours of labor. At 4:42 P.M. the placenta was delivered intact with a moderate amount of bleeding. At 6:00 P.M. the patient bled more than usual, and intravenous glucose and saline were given. At 7:30 P.M. profuse bleeding occurred, pulse 160 and blood pressure 50/0. Two pints of plasma and one pint of blood were administered. At 7:50 P.M. under gas-oxygen anesthesia, examination revealed an inversion of the uterus which was replaced and packed. At 8:15 P.M. her pulse was 145, blood pressure 90/70, and the patient's condition was fair. Another pint of blood was given. On the following day her condition was good, and the uterine packing was removed. Recovery was uneventful, and the patient was discharged in good condition eight days post partum. Her temperature did not go over 100° F. at any time. Six weeks post partum examination revealed the uterus in good position.

Summary

A method of manual replacement of the inverted uterus is described.

This method of replacement is simple and can be done immediately without increasing shock. As a matter of fact, shock and hemorrhage are relieved by this procedure.

General anesthesia is necessary and was used in all cases.

Nine cases of inversion of the uterus are reported.

Six cases or 67 per cent were primiparae.

The ages ranged from 19 to 30 years.

All cases but one showed marked shock and hemorrhage. These cases required from one pint of blood to as much as four pints of blood and three pints of plasma. One case was diagnosed immediately and the uterus was replaced within six minutes after inversion. There were no signs of shock or hemorrhage and further treatment was unnecessary on this patient.

In seven cases the third stage of labor lasted thirty-one minutes or less, in one case seventy minutes, and another two hours and thirteen minutes.

In six cases the period of inversion was short, varying from six minutes to five hours and thirty-five minutes. In one case the period of inversion was fourteen days, in another two months, and in a third, three months.

In two cases subsequent pregnancies were uneventful.

a living male child was delivered at 10:55 P.M. by low forceps under ether anesthesia. One ampule of ergotrate was given, and the perineum repaired. Twenty minutes later, after several attempts and marked pressure upon the fundus, the placenta presented itself at the introitus in an inverted umbrella fashion, and was removed from the vagina manually. During this removal it was found to be adherent to an inverted uterus. Profuse bleeding followed, and 1,000 c.c. of 100 per cent glucose were given intravenously. Many attempts were made to reduce the inversion, during which time the patient was under ether anesthesia, and the bleeding was profuse. I saw this patient about one hour after delivery. Her condition was poor, and she was still under anesthesia. The uterus was replaced manually and packed with gauze. The anesthesia was stopped, and ergotole and morphine were given. The patient was very restless and was moving around the table; her pulse very rapid, and her blood pressure was not obtainable. Oxygen was administered because of the marked cerebral anoxemia. Following a blood transfusion of 450 c.c. her condition improved. The next day, the pulse was still very rapid, there was marked pallor, and general condition poor. Another transfusion of 700 c.c. was given, and the uterine packing was removed. For the next five days the temperature remained between 100° and 102° F. Vaginal bleeding was moderate, and her general condition improved. She was discharged twelve days post partum in good condition, the uterus being anterior and well involuted.

CASE 5.—A. P. (South Nassau Communities Hospital), a white primipara, aged 23 years, was delivered by breech extraction at 3:34 A.M., Aug. 8, 1942, after twenty-nine hours of labor. The placenta was delivered without difficulty at 3:44 A.M. The patient bled profusely, was pulseless, and her blood pressure was 60/0. Plasma was given and the uterus was packed with iodoform gauze. Fifteen hundred cubic centimeters of plasma and 700 c.c. of blood were given. The condition improved very nicely, the packing was removed in thirty-six hours, and she was discharged on the twelfth day after delivery. Moderate bleeding continued after discharge from the hospital, and on Oct. 8, 1942, two months post partum, I saw this patient and examination revealed an inverted uterus. She was admitted to the hospital and the uterus was replaced. Temperature was 102° F. for twenty-four hours, then returned to normal. She was discharged in good condition five days after replacement.

CASE 6.—V. B. (South Nassau Communities Hospital), a white multipara, para i, gravida ii aged 28 years, was admitted on Feb. 5, 1943. After twenty-five hours of poor labor a living child was delivered by low forceps at 11:42 P.M. on Feb. 6, 1943. One hour and ten minutes later, after much difficulty, the placenta was delivered. I saw this patient at 2:00 A.M., at which time she was in severe shock. The vagina had been packed and there was slight bleeding present. One thousand cubic centimeters of plasma and 500 c.c. of glucose were given, and at 3:00 A.M., her pulse was improved and blood pressure 90/60. At 5:00 A.M., 700 c.c. of blood were given, the patient continued to bleed, and at 6:35 A.M. gas-oxygen anesthesia was administered, the packing removed, and the uterus found to be inverted. The uterus was replaced and packed. Five hundred cubic centimeters of plasma and 1,300 c.c. of blood were given during the next eighteen hours. Packing was removed in twenty-four hours, temperature 103° F., pulse rapid but good quality, and moderate abdominal distention existed. Temperature after five days became normal. Sulfathiazole was given during this period. The patient was discharged fifteen days post partum in good condition.

CASE 7.—S. E. (South Nassau Communities Hospital), a primipara, aged 23 years, was admitted on Dec. 22, 1944. The patient was delivered at 3:42 P.M. by forceps after ten hours' labor. At 5:55 P.M. the placenta was delivered, and was followed by a hemorrhage of about 1,500 c.c. I saw this patient at 7:30 P.M. in severe shock. Plasma was being given at the time and a total of four pints was administered. At 8:15 P.M. moderate bleeding was present, blood pressure 72/0. Vaginal examination revealed an inverted uterus. Gas-oxygen anesthesia was given, and the uterus was replaced and packed. At 8:45 P.M. the blood pressure was 72/0, pulse 136, and plasma was still being administered, the last of the fourth pint. Uterine packing was removed in thirty-six hours, and 500 c.c. of blood were given. The patient had a temperature of 101° to 102° F. for five days, and was discharged on Jan. 6, 1945, in good condition, fourteen days post partum.

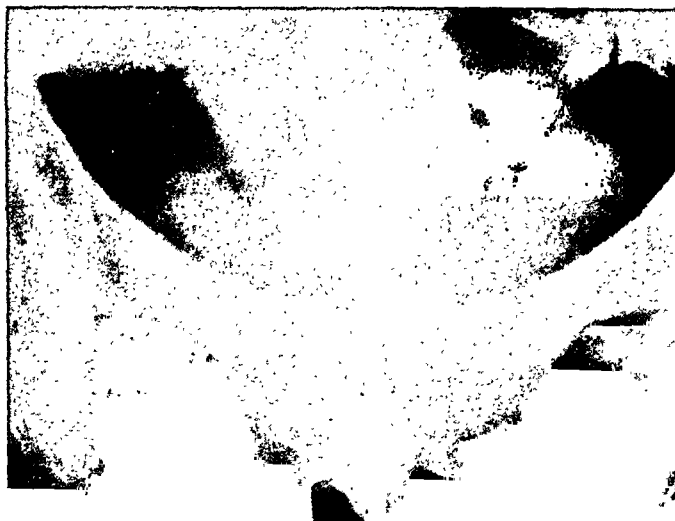


Fig. 1.—Uterine cavity is normal in size, shape, and position. There is no evidence of any filling defects. Several tiny sacs are seen extending from the superior surface of the uterine cavity. *Impression:* adenomyosis uteri.



Fig. 2.—The uterine cavity is normal in size, shape, and position. Several small projections are seen extending from the left side of the uterine cavity. *Impression:* adenomyosis uteri.

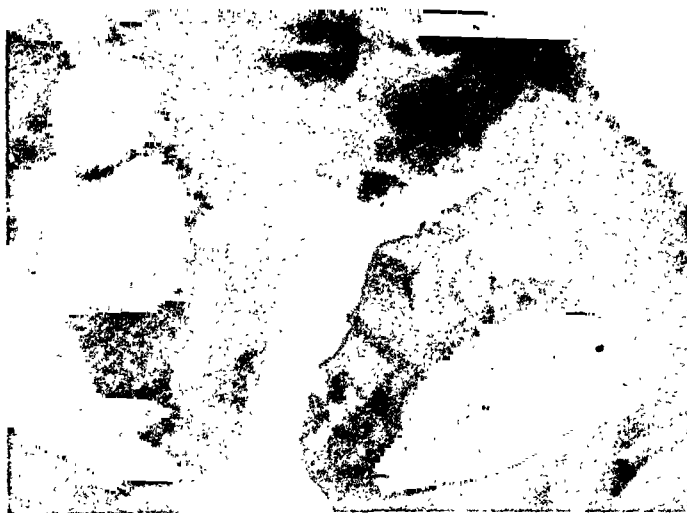


Fig. 3.—The uterine cavity is normal in size, shape, and position. There are several large sacs extending from the superior surface of the uterine cavity. Others are seen immediately above the cervical os. *Impression:* adenomyosis uteri.

ROENTGEN DIAGNOSIS OF ADENOMYOSIS UTERI

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ADENOMYOSIS of the uterus is a condition characterized by benign invasion of the endometrium into the uterine musculature associated with an overgrowth of the latter.¹ It differs from pelvic endometriosis in that whatever is responsible for the abnormal endometrial growth affects the uterine musculature as well. On section through such a uterus, the striking feature is this marked musculature overgrowth. A frequent, although not constant, feature on examination of the extirpated uterus is the presence of dark, hemorrhagic areas varying in size from 1 to 4 mm. in diameter and scattered discretely throughout the musculature. The latter represent islands of endometrium in which menstrual hemorrhage has occurred. This invasion of endometrium into muscle forms tubelike structures into which the radiopaque media may penetrate, producing according to our findings a rather characteristic roentgen film. Short, spiculelike structures extend especially from the superior surface of the uterus varying in size from 1 to 4 mm. and ending in very tiny sacs. This roentgen finding was noted in approximately 15 per cent of the cases of adenomyosis. A possible cause for failure of the dye to enter the endometrial channels in the other cases is the marked overgrowth of muscle which may act as a pinch-cock preventing the dye from going into the endometrial channels. Another possible cause for failure is the presence of clotted blood within the endometrial channels. We have made the diagnosis of adenomyosis by the above means twelve times in a series of three hundred hysterograms performed because of menstrual irregularity. These cases were confirmed by hysterectomy.

Some of the cases of adenomyosis found at operation which did not reveal the tiny sacs on review of the roentgenograms revealed an irregularity of the uterine border. This irregularity was more marked than was usually noted with hyperplasia of the endometrium. On pelvic examination, the uterus in these cases was usually globular and slightly enlarged. These findings would therefore suggest adenomyosis when the tiny sacs were not visualized. Adenomyosis can, on occasion, produce a filling defect within the uterus which simulates a submucous fibroid. Two such cases were encountered. The uterine walls, in these cases, were unusually thick and probably only permitted the dye to outline the periphery of the uterine cavity. Recently we have visualized the tiny sacs more frequently. A possible explanation may be the use of Skiodan acacia in preference to Lipiodol. Skiodan acacia is less viscous and probably enters the endometrial channels more readily than Lipiodol.



Fig. 6.—The uterine cavity is normal in size, shape, and position. Several small sacs extend from the superior surface of the uterine cavity.

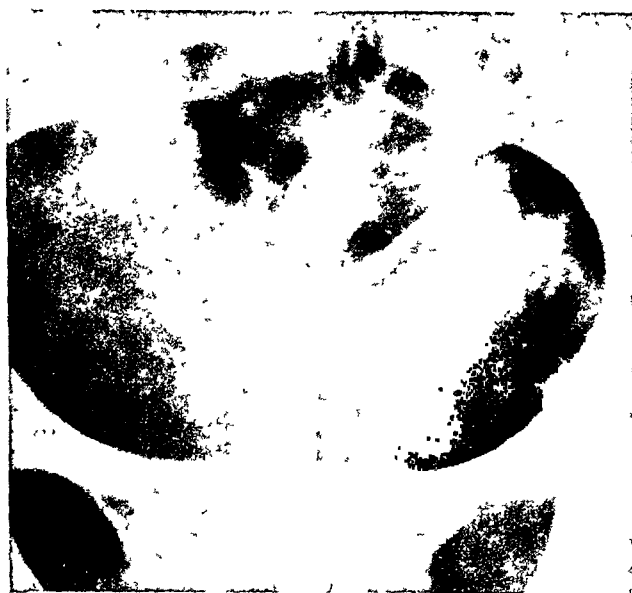


Fig. 7.—The uterine cavity is small. There is a concavity on the superior surface of the uterine cavity which can be due to an intramural fibroid but which is occasionally seen normally. Several small sacs are seen extending from the superior surface of the uterine cavity.



Fig. 8.—The uterine cavity is slightly enlarged, dextroverted. There are several small filling defects within the uterine cavity and tiny sacs extending from the border of the uterine cavity. *Impression: adenomyosis.*

Case Reports

CASE 1.—S. H., a 40-year-old woman, entered Mount Sinai Hospital with a chief complaint of profuse menstrual bleeding lasting eight to nine days and passing clots. Her present illness started six months ago with an increase in her periods. Her last two periods were very severe, lasting ten days and passing numerous clots. The remainder of the history was essentially negative.

Physical examination: The uterus was slightly enlarged, not tender. Both adnexa were not palpable. The cervix was not smooth. The remainder of the physical examination was negative. Hysterography revealed no evidence of any filling defects. Several tiny sacs were seen extending from the superior surface of the uterine cavity. A diagnosis of adenomyosis was made which was confirmed by the pathologic sections (Fig. 1).



Fig. 4.



Fig. 5.

Fig. 4.—Same case as above, revealing the sacs in the injected specimen.

Fig. 5.—Hysterography reveals the uterine cavity to be normal in size, shape, and position. Several sacs are seen extending from the uterine border.

CASE 2.—M. P., was a 36-year-old woman with the chief complaint of dysmenorrhea and menorrhagia of many years' duration. Pelvic examination disclosed an enlarged, globular uterus the size of an orange. Both adnexa were thickened and not tender. Numerous small nodules were palpated in the cul-de-sac. Hysterography revealed many small projections extending from the left side of the uterine cavity. A diagnosis of adenomyosis was confirmed by the pathologic sections (Fig. 2).

CASE 3.—L. F. was a 43-year-old woman with the chief complaint of dysmenorrhea since the onset of her periods and menorrhagia during the last four years. Pelvic examination disclosed the uterus to be enlarged to a two months' gestation due to multiple fibroids. Hysterography revealed several large sacs extending from the superior surface of the uterine cavity. Others were seen immediately above the cervical os. Hysterectomy and sections confirmed the diagnosis of a fibroid uterus with adenomyosis (Fig. 3). Fig. 4 reveals the sacs in the injected specimen.

CASE 4.—T. L. was a 32-year-old woman with the chief complaint of menorrhagia of six months' duration. Pelvic examination revealed the uterus to be enlarged to the size of a three months' gestation by multiple fibroids. Hysterography revealed several tiny sacs extending from the uterine border. (Fig. 5). One fairly large sac was seen above the cervical os on the right side. Hysterectomy and section confirmed the above diagnosis.

Conclusions

1. Hysterography is of great help in determining the presence of intra-uterine pathology.
2. Adenomyosis uteri can be occasionally diagnosed by hysterography, especially when the dye enters the endometrial pits which have invaded the uterine musculature.
3. The above findings has been seen more frequently since the use of Skiodan acacia.
4. Hysterography has been very helpful in the institution of more specific therapy.
5. There have been no reactions or ill effects from the use of Skiodan acacia in these cases.

Reference

1. Novak, E.: Gynecological and Obstetrical Pathology, Baltimore, 1940, The Williams and Wilkins Company.
1075 PARK AVENUE

CASE 5.—A. S. was a 36-year-old woman with the chief complaint of dysmenorrhea and a feeling of weight in her pelvis. Her periods were normal. Pelvic examination revealed the uterus to be enlarged to the size of a grapefruit. Hysterography revealed several small sacs extending from the superior surface of the uterine cavity (Fig. 6). Operation confirmed the diagnosis.

CASE 6.—R. R., a 48-year-old woman, was admitted with abdominal pain, menorrhagia, dysmenorrhea, and anemia. The uterus was enlarged and nodular. Endometrial biopsy revealed a proliferative endometrium. Hysterography revealed several tiny sacs in the superior portion of the uterine cavity (Fig. 7). Dilatation and curettage were done and the pathologic report revealed fragments of endometrium in a proliferative stage. She was admitted again one year later with a severe metrorrhagia for two months after four months after amenorrhea. Pelvic examination was similar to the previous admission. Hysterectomy was performed which revealed adenomyosis and small fibromyomas.



Fig. 9.—The uterine cavity is normal in size, shape, and position. A circular filling defect is noted within the uterine cavity. At operation, this was found to be due to thickened uterine musculature rather than to submucous fibroid.

CASE 7.—L. G., a 42-year-old woman, was admitted with the chief complaint of vaginal spotting for the last six weeks. Pelvic examination revealed the uterus to be slightly enlarged. Hysterography performed with Lipiodol revealed several tiny sacs extending from the border of the uterine cavity. In addition, numerous small filling defects were seen within the uterine cavity. Hysterectomy revealed adenomyosis (Fig. 8).

CASE 8.—S. A., a 28-year-old woman, was admitted with the diagnosis of menometrorrhagia of two years' duration. Recently the bleeding had become severe and the patient passed numerous clots. Pelvic examination revealed the uterus to be slightly enlarged. Both adnexa were not palpated. Hysterography revealed (Fig. 9) a filling defect occupying practically the entire uterine cavity. A diagnosis of a submucous fibroid was made. Dilatation and curettage were performed and, although the operator could feel a tumor, he was unable to remove it. Hysterectomy revealed a uterus that was slightly enlarged. The muscular layer was extremely thickened and bulged into the uterine cavity. Except for a very small endometrial polyp in the left upper quadrant of the uterine cavity, no further abnormality was noted. It was felt that the marked overgrowth of muscle produced a bulging into the uterine cavity which simulated a submucous fibroid. We have since encountered this finding in another case confirmed by operation.

In the months in which there was no prophylactic penicillin used, 45 cases developed a temperature of over 100.4° F. for more than twenty-four hours, giving a gross morbidity of 9.8 per cent. Compare this to the months in which prophylactic penicillin was used, when 21 cases developed the above temperature, giving a gross morbidity of 4.7 per cent. Table I shows that several of these cases were not due to infection in the genital tract, so if we include only those cases associated with lacerations or episiotomies, endometritis, parametritis and thrombophlebitis, we get a corrected morbidity of 7.4 per cent (34 cases) in the nonprophylactic penicillin group, as compared to 2.2 per cent (10 cases) in the prophylactic group. This is well below the average quoted morbidity of (5 to 7 per cent) and represents an improvement of over 50 per cent in the corrected morbidity of this hospital.

Table II attempts to portray the difference in morbidity between early and late risers during both nonprophylactic penicillin months and prophylactic penicillin months. There is a definite improvement in both early and late risers using prophylactic penicillin noted particularly in the late risers, in whom we have 13 per cent morbidity in the nonpenicillin group compared with 4.5 per cent in the prophylactic group. The effect is not so noticeable in the early risers, in whom the comparison is 6.8 per cent to 4.9 per cent. It should be noted that, where penicillin is not used, early rising cuts this morbidity in half, but where prophylactic penicillin is used, the early rising appears to make no difference.

TABLE II. EFFECT OF EARLY AND LATE RISING ON MORBIDITY DURING PROPHYLACTIC AND NONPROPHYLACTIC PENICILLIN MONTHS

	NONPENICILLIN			PROPHYLACTIC PENICILLIN		
	NO. CASES	MORBIDITY		NO. CASES	MORBIDITY	
		CASES	PER CENT		CASES	PER CENT
Early rising	235	16	6.8	225	11	4.9
Late rising	222	29	13	221	10	4.5

In Table III, the percentage of morbidity is shown by months for both nonprophylactic penicillin and prophylactic penicillin groups. In general, it shows no regular seasonal variation for either group. All months except July, September, and November show an improved percentage morbidity using prophylactic penicillin.

TABLE III. SEASONAL VARIATION OF PERCENTAGE MORBIDITY (100.4° F.)

	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN.
Non penicillin months	8.5	9.4	19.5	3.4	10.8	4.2	14.7	4.2	17.6	16.6
Penicillin months	6.3	0	8	4.5	5.8	10	2.1	5.2	0	6

Low-Grade Morbidity

It has been clearly shown that, when using the morbidity standard set by the American College of Surgeons, the use of prophylactic penicillin did reduce the maternal morbidity. However, as already stated, it is our intention to study further the maternal morbidity by selecting as a standard a temperature of 99.2° F. for over twelve hours excluding the first twenty-four hours. This low was selected for several reasons: (1) We believe that any rise of temperature above 99.2° F. should be considered a morbidity. (2) In many

THE PROPHYLACTIC USE OF PENICILLIN IN OBSTETRICS

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THE standard of maternal morbidity as set by the American College of Surgeons includes all cases with temperature of 100.4° F. or over for more than twenty-four hours, excluding the first twenty-four hours post partum. This does not include low-grade fevers below this temperature which may, in themselves, be evidence of some serious condition, yet are not included in the standard morbidity rate.

In an endeavor to discover a means to reduce this standard morbidity and at the same time the low-grade fevers mentioned above, a study was made in the Grace Maternity Hospital, Halifax, N. S., using prophylactic penicillin on all postpartum cases delivered by the vaginal route.

These patients were given 20,000 units of calcium penicillin intramuscularly every three hours for ten doses beginning immediately post partum. If the membranes were ruptured for more than twelve hours before delivery, the penicillin was started pre partum. In addition to the above, if the patient did develop a fever, the penicillin was continued as long as seemed necessary.

Four hundred forty-six cases delivered during the months of April, 1947, to January, 1948, both inclusive, received the above dosages of penicillin. The percentage morbidity of these cases was then compared with 457 cases delivered during the corresponding months of April, 1946, to January, 1947, both inclusive, in which no prophylactic penicillin was given. Temperatures were taken every four hours.

In this hospital for several years, there has been an opportunity to study the effects of early rising as compared to those of late rising. During the months of May, July, September, November, and January of both series, the patients were permitted to get up and walk around the bed on the day following delivery. On the alternate months, they did not leave their beds until the sixth day. In addition, the early risers were given a simple series of bed exercises. Reference will be made later in this paper to the effects of early and late rising on the morbidity rates.

TABLE I. INCIDENCE OF CAUSES OF MORBIDITY (OVER 100.4° F.)

	SAPRE- MIA	MAS- TITIS	INFECTED EPISIOT- OMY	PYELITIS	CHEST	PHLE- BITIS	OTHERS	NIL NOTED
No penicillin	13	6	3	8	4	0	1	10
Prophylactic penicillin	6	6	0	6	2	0	1	0

TABLE V. SEASONAL VARIATION OF PERCENTAGE MORBIDITY (99.2° F. OR OVER)

	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN.
Nonprophylactic penicillin	51.3	52.8	63.9	32.7	41.3	55.9	67.6	57.4	69.3	53.5
Prophylactic penicillin	40.4	13.1	32.4	36.3	56.8	32.5	43.4	36.8	27.5	42.0

TABLE VI. EFFECT OF EARLY AND LATE RISING ON MORBIDITY (99.2° F.) DURING PROPHYLACTIC AND NONPROPHYLACTIC MONTHS

	NONPENICILLIN			PROPHYLACTIC PENICILLIN		
	MORBIDITY			MORBIDITY		
	NO. CASES	CASES	PER CENT	NO. CASES	CASES	PER CENT
Early rising	235	119	50.6	225	71	31.5
Late rising	222	133	59.9	221	97	43.8

TABLE VII. INCIDENCE AND PERCENTAGE OF CAUSES OF MORBIDITY (99.2° F.)

	SAPREMIA			MASTITIS			INFECTED EPISIOTOMY			PYELITIS			CHEST			PHLEBITIS			OTHERS			NIL NOTED		
	MORBIDITY			MORBIDITY			MORBIDITY			MORBIDITY			MORBIDITY			MORBIDITY			MORBIDITY			MORBIDITY		
	NO. CASES	PER CENT		NO. CASES	PER CENT		NO. CASES	PER CENT		NO. CASES	PER CENT		NO. CASES	PER CENT		NO. CASES	PER CENT		NO. CASES	PER CENT		NO. CASES	PER CENT	
Nonprophylactic penicillin	55	12		35	7.6		13	2.7		11	2.4		8	1.7		0	0		9	1.9		121	26.5	
Prophylactic penicillin	30	6.7		39	8.9		3	.6		9	1.9		3	.6		1	.2		4	.8		79	17.7	

TABLE VIII. AVERAGE DAYS IN HOSPITAL

	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN.
Nonpenicillin months	10	10	10.4	9.8	10	9.6	10.2	9.8	10.8	9
Penicillin months	9.3	8.9	8.9	8.3	8	8.2	9.2	9.6	9.5	9.4

pathologic conditions, the temperature never rises to 100.4° F., yet may be the basis for serious complications arising after the first ten days post partum, a pelvic cellulitis or mastitis for example. (3) Selecting this low standard makes the taking of temperatures every four hours necessary. This is not practiced in many maternity hospitals and we feel that the peaks of temperature often reached in the afternoon are being missed.

During the ten months in which prophylactic penicillin was given, 168 patients developed a temperature of 99.2° F. or over for more than twelve hours, giving a percentage morbidity of 37.6 per cent. Compare this with the preceding ten months in which no prophylactic penicillin was used and in which 252 patients developed a temperature of 99.2° F. or over, giving a morbidity of 54.9 per cent. An improvement of 17.3 per cent was noted with the use of prophylactic penicillin.

Table IV attempts to show the influence of prophylactic penicillin in reducing the morbidity during operative procedures. During the months in which no prophylactic penicillin was given, 81 patients were delivered by forceps operation, of whom 46 developed a temperature of 99.2° F., giving a percentage morbidity of 54.1 per cent, about the same as the general morbidity of this group. Low forceps of this group were associated with a slightly higher morbidity of 58.2 per cent. Compare this with the prophylactic group, in which 68 patients were delivered by low forceps, twenty of whom developed the low standard temperature, giving a percentage morbidity of 29.4 per cent, considerably less than the general morbidity of this group (37 per cent). This would tend to suggest that prophylactic penicillin does tend to reduce the morbidity associated with forceps deliveries.

TABLE IV. RELATION OF MORBIDITY (99.2° F.) TO OPERATIVE PROCEDURES

	NONPROPHYLACTIC PENICILLIN MONTHS			PROPHYLACTIC PENICILLIN MONTHS		
	TOTAL CASES	MORBIDITY		TOTAL CASES	MORBIDITY	
		CASES	PER CENT		CASES	PER CENT
Forceps	81	46	54.1	68	20	29.4
Midforceps	2	1	50	0	0	0
Low forceps	79	45	58.2	68	20	29.4
Versions and extractions	1	1	100	0	0	0
Perineal repair	162	89	54.9	173	53	30.6

One hundred sixty-two patients received some form of perineal repair during the control group of months, of whom 89 developed the low-grade temperature, giving a percentage morbidity of 54.9 per cent. Compare this to the prophylactic group in which 173 patients received some perineal repair, of whom 53 developed the above temperature, giving the percentage morbidity of 30.6 per cent—a considerable difference of 24.3 per cent.

There was only one case of version and extraction found in this series, so no comparison could be made there.

Table V gives a monthly comparison of percentage morbidity (99.2° F. or over for twelve hours). In general, it shows a considerable improvement during the months in which prophylactic penicillin was used as compared with corresponding months in which no prophylactic penicillin was used. No explanation could be found for the reverse in July and August.

Under the term "others" we listed all causes of morbidity not listed, such as finger infections, etc. "Nil noted" included those cases for which we could find no obvious cause for the temperature. Nothing statistically important could be drawn from either of these.

Table VIII gives the average hospital days per month of both groups. These represent the time from the day of delivery to day of discharge. It was impossible to exclude certain cases who were detained for various reasons not associated with morbidity, as awaiting transportation, severe toxemias, etc.

During the control months, the average hospital stay was 9.9 days compared to 8.8 for the prophylactic group, representing a hospital day saved for each patient. This in itself is statistically important.

In this series, there were no allergic reactions which could be attributed to the penicillin.

In a recent article in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* (February, 1948), Pierce of Cincinnati produced somewhat the same results in reduction of morbidity using prophylactic penicillin in the form of vaginal suppositories.

Summary

1. Four hundred forty-six patients received prophylactic penicillin intramuscularly every three hours for ten doses beginning immediately post partum, with a morbidity rate due to genital tract infection of 2.2 per cent using the "standard morbidity" and 37.6 per cent using the low standard selected (99.2° F. for more than twelve hours).

2. In the control group of four hundred fifty-seven cases, the morbidity rate was 7.4 per cent using the "standard morbidity" and 54.9 per cent using the low standard.

3. The effect of prophylactic penicillin associated with both early and late risers was compared with the nonprophylactic-penicillin group, using both the "standard morbidity" and the low standard of 99.2° F. An appreciable improvement in percentage morbidity was noted during use of prophylactic penicillin on both early and late risers.

4. The seasonal variation of morbidity for both groups using both standards of morbidity was noted. In general, it shows no regular variation. The monthly improvement of morbidity under prophylactic penicillin is noted.

5. The relation of operative procedures to morbidity was noted and the effect of prophylactic penicillin in reducing this morbidity studied. The percentage morbidity during operative procedures was definitely less with the use of prophylactic penicillin.

6. A study of the incidence and percentage of the causes of morbidity was made and the effect of prophylactic penicillin in reducing the incidence of these various diseases. The improvement was noted chiefly in those cases associated with genital tract infection. Fewer patients developing a temperature of 99.2° F. went on to higher temperatures.

7. Average hospital days per patient of both groups were compared.

There appeared to be little seasonal variation, the highest percentage morbidity being in October and December. This agrees with the general opinion that in winter months when respiratory infections are more common, we can expect to have a somewhat higher morbidity. However, with the use of prophylactic penicillin, the only real variation was in August, at which time the temperature rose higher than any other month—for which no explanation is apparent.

Table VI compares the percentage morbidity of early and late risers during penicillin and nonpenicillin months. Early risers in the control group exhibit a 50.6 per cent morbidity, compared to 31.5 per cent under prophylactic penicillin, an improvement of 19.5 per cent. Late risers in the control group exhibit a 59.9 per cent morbidity, compared to 43.8 per cent morbidity under the prophylactic group—an improvement of 16.1 per cent.

In Table VII is shown the incidence and percentage morbidity of the various causes of the low-grade morbidity studied for both prophylactic and nonprophylactic groups. The greatest variation is seen in those conditions arising primarily from infection of the genital tract, i.e., as already noted, infected episiotomy or laceration, endometritis, parametritis, and thrombophlebitis.

Twelve per cent of the total patients of the control group became morbid due to sapremia, compared to 6.7 per cent during the prophylactic penicillin months. This represents a decrease of almost 50 per cent of cases developing the commonest form of genital infection (postpartum) by the use of prophylactic penicillin. This is statistically important.

Further, of the 55 patients of the control group who developed sapremia, 13, or 23.6 per cent went on to develop a temperature of 100.4° F. or over for more than twenty-four hours. Compare this with the prophylactic group where, of the 30 patients suffering from sapremia, 5, or only 16.6 per cent went on to develop a temperature of 100.4° F. or more for more than twenty-four hours. This may be significant although the number is not large enough.

During the control months, there were 162 perineal repairs, of which 13 became infected. Thus, 2.7 per cent of the control group developed a morbidity due to infected episiotomies. Compare this to the prophylactic group in which only 3 cases out of 173 with repairs developed an infection, representing 0.6 per cent of the entire group. This would seem to suggest that prophylactic penicillin has decreased the percentage morbidity due to infected episiotomies.

There was only one case of thrombophlebitis developing on the sixth day post partum. This patient was one of the late risers but had received prophylactic penicillin. No comparison is possible.

Prophylactic penicillin did not appear to have any appreciable effect on the incidence of breast infections. Out of 446 patients using prophylactic penicillin, 35 patients, or 7.6 per cent developed various degrees of mastitis. Compare this with 39 cases, or 8.9 per cent out of 457 cases not using prophylactic penicillin. The difference is not significant. However, 4 patients, or 10.2 per cent of the 35 cases, went on to develop a temperature of 100.4° F. for more than twenty-four hours. Compare this to the prophylactic group in which 2 patients, or 5.1 per cent of the 39 patients, developed this higher temperature. In neither group could we find evidence of abscess formation while in hospital.

As one would expect, there is no appreciable change in the incidence of pyelitis. Two and four-tenths per cent of the control group developed a morbidity due to pyelitis, as compared to 1.9 per cent of the prophylactic group.

Chest infections showed somewhat the same results—very little difference noted. Eight patients, or 1.7 per cent of the control group, developed a temperature due to chest infections compared with three patients, or 0.6 per cent of the prophylactic group. This is not significant.

Radium, 2,400 mg. hr., was applied to the cervical canal April 16, 1937. A biopsy report at this time was not made.

Aug. 21, 1937, 2,400 mg. hr. of radium were applied to the cervical canal. At this time, there was an extensive malignant growth occupying the depth of the vagina. The cervical canal was represented by a craterlike opening surrounded by red, friable, easily bleeding tissue. The growth had extended into all contiguous pelvic structures. A biopsy was taken at this time. Following this last admission the patient was lost sight of.

The second case was Mrs. M. M., aged 65 years, a white woman who was admitted Aug. 11, 1936, with a chief complaint of whitish vaginal discharge and vaginal bleeding. These complaints had been present for a period of four months. The examination disclosed on the left portion of the cervix a whitish mossy-appearing growth slightly smaller than a dime. It bled easily on trauma. It was raised 1 mm. from the smooth surface of the cervix. There were some hardened points on the posterior vaginal wall. The preoperative diagnosis was leucoplakia of the cervix. The biopsy showed a growth of stratified squamous epithelium beneath which was a dense chronic inflammation. The growth rested on a dense fibromuscular stroma. There was an ulceration at one point. The epithelium grew in long sheets which extended into the underlying stroma. The nuclei of the cells were large and hyperchromatic. In one area there were isolated islands of cells which presented invasive tendencies. The diagnosis was leucoplakia of the cervix with beginning malignant changes.

Radium, 1,900 mg. hr., was applied to the cervical canal following cautery resection of the cervical growth on Aug. 12, 1936. This patient had Parkinson's disease and pronounced arteriosclerosis.

On Feb. 2, 1937, the cervix was adherent to the posterior vaginal wall by light adhesions which were separated. There was some redness around the os with leucoplakia present in this area and also in the posterior vaginal wall. The cervical canal was readily dilated.

A biopsy was done Feb. 5, 1937, which showed intense scarring of the cervix. No tumor cells were seen.

On Feb. 5, 1937, 2,500 mg. hr. of radium were applied in the cervical canal.

The patient continued to have bleeding from the cervix and vaginal tissue with a considerable purulent discharge from the uterus and cervix. The appearance grossly was that of malignancy.

On July 27, 1937, there was induration extending outward into each broad ligament. It was diagnosed as Class IV carcinoma. On July 30, 1937, radium (2,400 mg. hr.) was again applied.

The patient was seen March 8, 1938, and no evidence of residual malignancy was found.

The third case is that of Mrs. P. C., aged 36 years, a white woman who was admitted with a history of metrorrhagia and leucorrhea for which she had a cauterization of the cervix March 27, 1939. No biopsy was taken. The preoperative diagnosis was chronic cervicitis with erosion and leucoplakia of the cervix uteri.

The clinical course following this procedure was satisfactory without the development of malignancy.

The fourth case was that of Mrs. W. S., aged 39 years, a white woman who was admitted Oct. 22, 1939, with complaints of meno-metrorrhagia, vaginal discharge, and lower left quadrant abdominal pain. All of these symptoms were of approximately five months' duration. There had been two full term pregnancies and no miscarriages. Her menopause was at age 34 years following a surgical operation. The cervix was enlarged, bilaterally lacerated, and showed Nabothian cysts as well as an area of erosion. There also was a grayish-white area of leucoplakia near the right end of the tear. The cervix was covered with purulent exudate. The uterus, tubes, and ovaries were essentially negative, excepting for an enlarged, cystic, tender left ovary. The patient was discharged without operation. No follow-up could be obtained.

LEUCOPLAKIA OF CERVIX UTERI

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LEUCOPLAKIA of the cervix uteri is of practical importance for two reasons: (1) it may represent an area of noninvasive carcinomatoid changes, or (2) it may represent the first visible manifestation of an early established cancer. The problem of cervical leucoplakia and its conversion into established cancer is a vexatious one. The infrequency of the diagnosis of this condition in the cervix uteri has stimulated a review of the case records in the record department of the Elizabeth Steel Magee Hospital with some interesting findings.

Fourteen cases of leucoplakia of the cervix uteri were encountered from 1927 to 1946 in the Elizabeth Steel Magee Hospital. This number occurred in 103,685 gynecologic admissions. These fourteen cases were discovered among 8,906 patients having cauterization of the cervix and 1,221 of them who had tissue excised for biopsy purposes.

Résumés of the clinical records of these fourteen cases of leucoplakia follow. The first is that of Mrs. H. H., aged 43 years, a white woman who was admitted to the Elizabeth Steel Magee Hospital June 1, 1936, with a chief complaint of vaginal bleeding, loss of weight, fatigue and pain in the lower abdomen. Atypical vaginal bleeding had been present for ten months. The patient had had two miscarriages, one in 1918 and one in 1924, each approximately at two months, following a full-term pregnancy with a spontaneous delivery in 1919.

The examination was essentially negative except for the presence of a large fungating, extremely friable, freely bleeding growth involving the entire cervix. The uterus was not enlarged. On rectal examination there was some thickening of the base of the left broad ligament. The preoperative diagnosis was cancer of the cervix, but a frozen section of a biopsy specimen indicated it was nonmalignant. The permanent section showed dense, thick, stratified squamous epithelium which in areas was replaced by columnar epithelium. There were large prolongations of the stratified epithelium deep within the myocervium. These were composed of typical stratified squamous cells limited by a basement membrane and showing no invasive tendencies. Surrounding these areas of stratified squamous epithelium was a rather intense infiltration of round cells with a few eosinophiles and polymorphonuclear leucocytes.

On June 6, 1936, a diagnosis was made of leucoplakia of the cervix. Radium, 3,600 mg. hr., was applied to the cervical canal. The patient's course following radium was stormy. The result of the radiation therapy was satisfactory and the note in the clinic Oct. 20, 1936, indicated the cervix as roughened and nodular but freely movable. It bled readily. Cautery amputation of the cervix and other radium treatment were advised.

On Nov. 7, 1936, 3,000 mg. hr. of radium were applied to the cervix. On Nov. 13, 1936, a biopsy of the cervix was again made, a section of which showed microscopically islands of squamous epithelium growing in large sheets, invading the underlying tissue. The cells were large and pleomorphic and showed numbers of mitotic figures. The diagnosis was squamous-cell carcinoma of cervix (noncornifying type).

The eighth patient was Mrs. S. W., aged 44 years, a white woman who was admitted June 29, 1942, with a chief complaint of backache and leucorrhea which had been present for a period of one and one-half years. The examination disclosed a cervix moderately enlarged, bilacerated, and which contained several white, raised areas which did not stain when Churchill's iodine was applied.

The pre-operative diagnosis was cystocele, rectocele, and leucoplakia of the cervix. On July 1, 1942, an anterior colporrhaphy, Hegar perineorrhaphy, hemorrhoidectomy, total hysterectomy, and appendectomy were performed. The pathologic diagnosis on July 1, 1942, was chronic endocervicitis with Nabothian cysts, leucoplakia of cervix, endometrium—late lutein phase, mild chronic metritis, chronic interstitial appendicitis. Histologic sections of cervix were partially covered by keratinized columnar and stratified squamous epithelium. At the region of the pale white plaque noted grossly, the stratified squamous epithelium sent a few short narrow pegs toward the deeper tissues. There was also a low-grade chronic inflammatory reaction associated with the above.

The ninth case was Mrs. E. M., aged 62 years, a white woman who was admitted with chief complaints of incontinence of urine and prolapse of the pelvic organs. These complaints were of six months' duration. There was relaxation of the perineum and a cystocele with a second-degree prolapse of a small uterus. The cervix was hypertrophied with a clean external surface. The operation on Oct. 16, 1942, was a Manchester anterior colporrhaphy, repair of enterocele, amputation of the cervix, and a Hegar perineorrhaphy. The pathologic diagnosis was chronic endocervicitis and early leucoplakia with keratinization. Histologically, the section was composed of stratified squamous epithelium which in one place was very thick and covered on the surface by keratin. A low-grade chronic inflammation was associated. The patient when last seen on Dec. 8, 1942, was free of complaints.

The tenth patient was Mrs. M. D., aged 29 years, a white woman who was admitted June 28, 1942, with a history of pain in the lower abdomen and back of five months' duration. The clinical diagnosis was chronic cervicitis. The operation on June 30, 1942, was biopsy of the cervix and cauterization of the cervix. The laboratory diagnosis was leucoplakia of cervix uteri. Histologic sections of cervix showed a surface covered with a heavy layer of keratinized stratified squamous epithelium. The epithelium showed papillary infoldings. There was an associated chronic inflammatory reaction.

A second admission on Feb. 11, 1945, because of leucorrhea of six months' duration resulted in a clinical diagnosis of leucoplakia of the cervix and postcauterization stenosis of the cervix. On Feb. 13, 1945, a biopsy of the cervix, cauterization of the cervix, and insertion of stem pessary were performed. Histologically, a section of the cervix again showed surface epithelium thick and heavily keratinized. The pathologic diagnosis was chronic endocervicitis. The patient's condition was satisfactory when last seen.

The eleventh patient was Mrs. A. S., aged 42 years, a white woman who was admitted Sept. 27, 1943, complaining of a low back pain of five years' duration. An examination disclosed a complete prolapse of the uterus associated with a cystocele, rectocele, and relaxation of the perineum. The cervix was lacerated and presented a zone of erosion about the external os. The uterus was small. The patient had an anterior colporrhaphy (Manchester type); a Sturmdorf amputation of the cervix, and an Emmet perineorrhaphy on Sept. 29, 1943. The laboratory diagnosis was leucoplakia of the cervix with metaplasia. Histologic section showed the surface epithelium to be thick and covered with keratin. It showed beginning proliferation of the deep layers at the external os where active metaplasia was seen. A low-grade chronic inflammation was present. When last seen April 3, 1944, the patient's condition was satisfactory.

The twelfth case is that of Mrs. E. D., aged 71 years, a white woman who was admitted July 15, 1945, with a chief complaint of protrusion of the pelvic organs from the vagina. An examination disclosed a third degree prolapse of the uterus and a relaxed and lacerated perineum with rectocele. The patient had had on Aug. 8, 1944, a Watkins Interposition operation, an amputation of the cervix, and a Hegar perineorrhaphy. The pathologic

The fifth case was that of Mrs. M. S., aged 61 years, a white woman who was admitted with a history of vaginal bleeding over a period of twenty months without having had a pelvic examination. She had had three pregnancies, two of which were full term and one a miscarriage at five months.

The examination disclosed the cervix to be three times normal size. The right side of the cervix was occupied by a granular, friable, freely bleeding, somewhat irregular mass with a narrow rim of normal-appearing cervical tissue surrounding it. There was induration of the base of each broad ligament, more marked on the left side. The uterus was enlarged to two and one-half times its normal size. The adnexa were not palpable.

Histologic diagnosis on Sept. 12, 1936, was leucoplakia with early malignant degeneration. The section was covered by stratified squamous epithelium which was quite thick with broad epithelial pegs. The epithelium had broken through the basement membrane and was extending into the underlying tissue in many places.

A second biopsy on Sept. 26, 1936, showed the same type of reaction. There were applied to the cervix 2,400 mg. hr. of radium from Sept. 26 to Sept. 28, 1936. From Oct. 2 to Oct. 4, 1936, 2,400 mg. hr. of radium were applied to the cervix. Excessive bleeding from the cervix followed this treatment. She had a repair of an incarcerated hernia on Jan. 7, 1937.

The next admission was April 13, 1940, with a history of having had constant bleeding for four months. She was suffering from a severe secondary anemia. The examination at the time of this admission revealed a plaque of apparent carcinomatous tissue in the upper vagina near the site of the cervix. The growth extended along the anterior vaginal wall into the bladder and through the pelvis forming a characteristic frozen type of pelvis. A biopsy was performed on April 16, 1940, which was reported squamous-cell carcinoma of the cervix. The section revealed irregular sheets of squamous epithelial cells growing in all directions. Mitotic figures were numerous. Small early pearl-like formations were present (atypical cornifying type). She received 600 r. onto the cervical site through the intracavitary cone and 2,400 r. externally over the pelvis.

The patient was discharged to her home and her condition was improved when last heard from in November, 1940.

The sixth case was that of Mrs. V. P., aged 40 years, a white woman who was admitted June 18, 1941, with a history of right-sided pelvic pain and urinary incontinence.

The examination disclosed an enlarged, cystic, bilacerated cervix with two small areas of leucoplakia which showed a positive Schiller test. The uterus was enlarged and there was some thickening of the parametrium. On June 23, 1931, the patient had a dilatation and cauterization of the cervix and Sturmdorf amputation with a Manchester anterior colporrhaphy and perineorrhaphy. The microscopic diagnosis from cervical tissue was active metaplasia of cervix, chronic endocervicitis with Nabothian cysts. The patient when last seen in the dispensary Aug. 28, 1941, was in good health.

The seventh patient was Mrs. M. A., aged 45 years, a white woman who was admitted May 21, 1942, with a complaint of pain in the lower abdomen and menorrhagia. The latter complaint had been present for the previous sixteen months. Her mother and sister had had cancer of the breast. The patient's breasts were negative. There was a firm movable mass in the pelvis reaching to three fingerbreaths below the umbilicus. The cervix uteri was lacerated, cystic, and showed the scars of two previous office cauterizations. On the left side of the angle of the cervix was an enlarged patch of white epithelium extending from the os to the periphery of the cervix. This could not be scraped off readily. It was diagnosed as metaplasia or leucoplakia. Preoperative diagnosis on May 22, 1942, was chronic cystic cervicitis, questionable leucoplakia of cervix, leiomyomas of the uterus, and endometriosis of left ovary. The operation was biopsy of cervix, cautery amputation of cervix, supravaginal hysterectomy, and left salpingo-oophorectomy. A microscopic section of the cervix showed in one area the squamous epithelium to be moderately thickened, sending long pegs of epithelium into the underlying tissue. The patient was free of evidence of pelvic disease on Nov. 16, 1944. A cystoscopic examination at this time was negative.

cent) out of these fourteen patients diagnosed as having leucoplakia of the cervix uteri developed carcinoma of the cervix at a future time. Two of these four patients having carcinoma of the cervix had this condition at the time of first biopsy. The series of cases given is small and consequently no positive accurate conclusions can be drawn. However, from following patients having such lesions, it is our impression that a very definite relationship exists between leucoplakia of the cervix and subsequent malignant growth.



Fig. 1.

Fig. 1.—Leucoplakia of the cervix showing thickening of the epithelium with rete peg formation and superficial areas of ulceration. Chronic inflammatory cells are seen beneath the epithelium. Very little keratin is present on the surface.



Fig. 2.

Fig. 2.—Noncornifying squamous-cell carcinoma of the cervix with typical epithelial-cell architectural pattern in contrast to section shown in Fig. 1.

Conclusions

1. A pale or white, slightly raised, discrete, circumscribed area, appearing on a background of pale pink cervical mucosa should be regarded with suspicion. These areas can readily be detected with a naked eye, rendering the use of a colposcope unnecessary. All such areas should be biopsied.

2. A leucoplakic lesion of the cervix is potentially malignant and should be regarded and treated as such.

3. A blanched, thickened area of epithelium on the cervix is more significant in a patient during the reproductive period of life than following the menopause.

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diagnosis on the portion of the cervix submitted was leucoplakia of cervix with mild keratinization and chronic cervicitis with ulceration. The histologic picture revealed the continuity of the stratified squamous epithelium to be interrupted by areas of ulceration containing necrotic tissue, hemorrhage, and polymorphonuclear leucocytes. The stratified squamous epithelium was thickened and keratinized. Lymphocytes had infiltrated the wall. In October, 1944, there developed an enterocele which was repaired Oct. 31, 1944. The patient has remained well to date.

The thirteenth patient is Mrs. E. W., aged 38 years, a white woman who was admitted Feb. 18, 1944, with a chief complaint of pain in the right lower abdominal quadrant and dysentery. The physical examination was essentially negative. It is noted that the cervix was nulliparous in type and presented a small white area adjacent to the os which did not rub off. The uterus was retroverted and fixed. The adnexa were tender and there were very tender nodules in the cul-de-sac. The findings were suggestive of endometriosis. The patient ran a moderate temperature. She had a leucocytosis and a rapid sedimentation rate. On March 15, 1944, with a preoperative diagnosis of chronic cervicitis (possible thrush infection), bilateral subacute salpingitis, and cystic left ovary, the following operation was performed: biopsy and cauterization of the cervix, bilateral salpingectomy, left oophorectomy and supra-cervical hysterectomy. At the time of operation, the above-mentioned whitish plaque in the surface of the cervix was considered to be due to a *Monilia* infection. A biopsy was taken from this point, a report from which is included in the following. At the time of operation both tubes were enlarged and surrounded by dense fibrous adhesions. The ovaries were cystic. The pathologic report was endometrium-follicular phase, chronic perimetritis, leucoplakia of cervix uteri with beginning surface carcinoma, marked chronic salpingitis and perisalpingitis, cystic follicles of ovary with chronic perioophoritis. The histology of the cervical biopsy showed thick keratinized surface epithelium with the cells in the thicker portions showing metaplastic changes. In the metaplastic areas the epithelial cells had taken on distinct pleomorphic changes, presenting a typical picture of a leucoplakia of the cervix with beginning surface carcinoma. No further treatment was given this patient and when last seen her condition was satisfactory.

The fourteenth patient was Mrs. M. B., aged 52 years, a white woman who was admitted March 26, 1945, with a chief complaint of a bloody vaginal discharge, which had been preceded by a period of amenorrhea of approximately eight months' duration. The examination was essentially negative, except for the presence of a cystic cervix containing a polypoid mass. This mass completely filled the cervical os. A cholecystogram, March 30, 1945, disclosed the presence of gallstones with a preoperative diagnosis of a cervical cyst and cholelithiasis. The following operation was performed: dilatation and curettage, removal of cervical cyst, cauterization of cervix, and cholecystectomy. The laboratory diagnosis on April 1, 1945, was endometrium-senile type, chronic endocervicitis with Nabothian cysts and beginning leucoplakia, and chronic cholecystitis with cholelithiasis. The cervix histologically showed surface epithelium which was thick in places and beneath which were areas of dense chronic inflammation. The patient at the time of last examination was in good condition.

Summary

Fig. 1 demonstrates a leucoplakia of the cervix uteri and presents a rather sharp contrast in the cellular architectural pattern to that shown in Fig. 2. The latter demonstrates a typical noncornifying squamous-cell carcinoma of the cervix uteri. The thick keratinized epithelium referred to many times in this report, together with an area of superficial ulceration and "rete peg" formation are shown in Fig. 1. For many years speculation concerning the relationship of leucoplakial epithelial thickening to subsequent malignant changes has existed. This relationship has not yet been proved, but in many cases certainly seems to exist.

In 103,685 gynecologic admissions, there were 14 cases diagnosed as leucoplakia of the cervix uteri. It is worthy of note that four (28.5 per

minutes. The supernatant fluid is discarded; the precipitate is ground up with five to ten c.c of N/10 sodium hydroxide. The mixture is centrifuged, and the supernatant fluid is poured into a test tube where it is neutralized with 20 per cent hydrochloric acid, using phenolphthalein as an indicator. 2.5 c.c. of this is then injected into the dorsal lymph sac of a male frog. The preparation of the concentrate takes less than one-half hour. The frogs were, at first, kept in individual covered glass dishes. More recently they are kept in covered glass funnels, having a diameter of five to six inches. In this way, the urine is collected in beakers, and it is very simple to catch a recently passed drop of urine from the funnel tip. If none has been passed, disturbing the animal, or gentle handling, usually produces urination. The urine is examined approximately every hour for four hours, or less if an earlier positive is obtained. Positive tests were occasionally obtained as early as forty minutes after injection, though no effort was made to find out how early spermatozoa might appear in the urine. Contrary to the experience of Robbins and Parker, in a few instances, urine which contained no spermatozoa at two hours were positive at four. While in most positive cases, the numbers of spermatozoa found were large, and frequently in aggregations as pictured by Robbins and Parker, there were a number of cases, particularly in very early pregnancies, where the numbers were very small, and the drops of urine had to be carefully searched under the microscope. The necessity for using more than one frog, as suggested by both groups of previous investigators, is confirmed; occasional frogs which did not react were encountered, and quantitative differences in reactivity were frequently noted.

Both previous reports stressed the fact that information was lacking about any possible seasonal variation in response to pregnancy urine. Both reports had dealt with winter frogs. Robbins and Parker speculated if special precautions might have to be taken during the breeding season. Glass and Rugh⁵ have described for *Rana pipiens* a single annual maturation cycle for spermatozoa, starting after the breeding season and completed in November. The mature spermatozoa are stored in the seminiferous tubules until release during the breeding season. Rugh⁶ has expressed doubt that sufficient numbers of spermatozoa were available for release during the summer months to permit the use of the male *Rana pipiens* as a pregnancy test animal. However, their illustrations indicate that spermatozoa are present in the seminiferous tubules during the summer months; the results hereinafter described indicate that they are released under gonadotropic stimulation. The first two reports dealt with results with winter frogs, when large numbers of stored spermatozoa are ready for release. The tests herein reported were run during the spring and summer. The impression has been obtained that in August the frogs emitted smaller numbers of spermatozoa following injection of pregnancy urine. Almost never in August were aggregated numbers of spermatozoa, as pictured by Robbins and Parker, seen, and as had been so frequently seen in earlier months.

One unexpected source of error was encountered during the progress of the investigation. The work was started during the breeding season when the sexual differences of the frogs were striking. As summer approached, the dimorphism became less striking, and in some individuals it was difficult to be certain of the sex; in some instances errors were made. The male is characterized by thicker, pigmented thumbs, and the presence of air sacs, which usually inflate during croaking. To obviate this difficulty, as well as for the reasons cited by Robbins and Parker, the frogs were sacrificed at the end of a test, and their gonads were examined. (Probably with greater experience, the error of sexual differentiation will become very low. Male frogs were ordered from the dealers; one of the two dealers with whom I have had experience has been much more successful in sending a very high percentage of male animals.)

THE USE OF THE MALE LEOPARD FROG (*RANA PAPIENS*) AS A PREGNANCY TEST ANIMAL*

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EARLY in 1948, Wiltberger and Miller⁷ briefly reported the use of the male frog *Rana pipiens* in a test for pregnancy. They reported no false negatives in the first trimester of pregnancy, and no false positives when using the urine from nonpregnant women and from men. Two hundred animals were used in the tests. As the technique described was simple, the test animal easy to obtain and relatively inexpensive, and the reported results extraordinarily accurate, it was decided to put the method to clinical test.

Between March 3 and August 31, slightly over 100 urines from patients were examined. During the progress of this work, the paper of Robbins and Parker⁵ appeared, reporting essentially the same results, using essentially the same technique as that described by Wiltberger and Miller. In 122 urines examined, they reported one false negative in 78 known pregnancies. Ten normal, menstruating controls and 34 cases of amenorrhea, negative by Friedman or Aschheim-Zondek tests, were all frog negative. Galli-Mainini and others^{1, 2, 4} have similarly used South American male toads.

Technique

As originally described, 5 c.c. of untreated morning urine were injected into the dorsal or lateral lymph sacs of two or more male frogs (*Rana pipiens*). The frogs were placed in separate glass jars, and, two to four hours later, the accumulated urine was examined microscopically for the presence of spermatozoa. The test animals were reused in four or five days. Robbins and Parker used essentially the same technique, except that they filtered the urine, and took cloacal smears, beginning one hour after injection. They reported some of the urines toxic and killing the frogs before a positive reaction could be obtained. To obviate this, they suggested injecting the urine in divided dosage.

At the beginning, I followed the technique as outlined by Wiltberger and Miller, but very soon was discouraged by the number of animals killed by the injections. As it appeared that the volume of fluid injected might be a factor in the death of animals, it was decided to try a concentration-detoxification method. This has proved most successful.

The technique used is as follows: 100 c.c. (if somewhat less is available, it is diluted to 100 c.c. with water) of morning urine is placed in a stoppered graduate, adjusted to pH 4 with 20 per cent hydrochloric acid, 5 c.c. of a hydrous aluminum silicate adsorbent† added, and the mixture well shaken by hand. It is allowed to stand for ten minutes, the supernatant fluid is discarded, and the remainder transferred to a centrifuge tube and centrifuged for about three

*Part of the cost of animals was defrayed by a grant from the Gynecology Department Research Fund.

†"Adsormone," purchased from Louis C. Herring & Co., Orlando, Florida. Detailed directions for its use accompany the material.

because the patient had begun to bleed. At this time, the frog test was negative. A rabbit test was not done. The patient subsequently aborted. Probably this should not be classified as a false negative. Placental death may have occurred previous to the second test. One patient on whom the frog test was negative and the rabbit weakly positive, on several occasions passed some decidua tissue, subsequently this patient aborted.

Discussion

The results herein reported confirm in essential details those previously reported with the male frog. There have been no false positive tests. A number of false negative tests were obtained, more than had been previously reported using either the male frog^{5, 7} or male toad.^{1, 2} However, the method was here put to more severe test inasmuch as the routine cases of hospital and office practice were utilized, and the more difficult clinical problems subjected to study. Examination of the false negatives show that all but two of them occurred after the last week in June. The two early ones were a missed abortion in which the rabbit test was only weakly positive; and one very early pregnancy, in which a parallel rabbit test was not performed. It might well be that the false negative reactions in the later cases are due to the lesser reactivity of the frog during the early phase of the maturation cycle, when numbers of stored spermatozoa are presumably few. The observations of Glass and Rugh are based on very few animals at each month of the cycle, and little information is available on the extent of individual variations. There have been numbers of instances, in confirmed positive cases, in which only one of the two frogs injected emitted spermatozoa under the stimulus of pregnancy urine. Further experience might teach that during the summer months, perhaps June through September, more than two frogs should be injected, and perhaps also a more concentrated urine extract should be used.

In spite of theoretical objections that the test would not work during summer months,⁵ it has proved most useful. It has been utilized as a guide in the handling of several cases of suspected ectopic pregnancy, in which the rapidity with which an answer could be obtained was of clinical importance. In several instances, a test run in the forenoon gave an answer before an operation scheduled tentatively for early afternoon. I can confirm, from the experiences of several of our obstetricians and gynecologists, the prediction made by Robbins and Parker that "the rapidity that it affords makes of the test an emergency procedure of possible benefit in difficult diagnostic problems."

The test is simple and inexpensive. The preparation of the urine and the injection of the frogs can be done by the average well-trained technician. Spermatozoa, when they are numerous, are unmistakable. When they are few, more experience is necessary for their recognition. Frogs are cheap, and the use of Adsormone adds little to the cost of the test. No special laboratory equipment is required. The frogs are stored in wire-mesh-covered five-gallon discarded metal drums, and kept in or over a sink. Water trickles through, and escapes from holes punched in bottom and sides. Frogs, as a rule, are kept for a week or less. During the summer months, if they are kept longer, "red-leg" becomes a problem. The differentiation of sex, although in some animals difficult, is not too serious a difficulty if each frog is checked by dissection after the test is completed. When one frog is negative, and the other a female, the test can be repeated very quickly. When frogs are certainly male (inflated air sacs), it is possible to utilize them again, as was done by Wiltberger and Miller. On several occasions, following a negative test, the same frogs were injected one to three days later with urine from known pregnancies, and positive tests were obtained. I feel, however, as stated above, that it is better to use frogs only once, and to sacrifice them after each test.

Results

One hundred-fourteen specimens of urine (from 104 individuals, including one male suspected of having a testicular tumor) were examined. Fifty-five positive frog tests were obtained, which were confirmed either by a Friedman test or by clinical signs of pregnancy. Positive tests were obtained as early as, in one case, the thirty-fourth day, in another, the thirty-seventh day of a cycle. In the former, a concomitantly performed rabbit test was negative; the frog test was very weakly positive; only rare spermatozoa were found in the urine of one of the two frogs injected. The woman is clinically pregnant. In the latter, artificial insemination had been performed on the fifteenth day, counting from the first day of the last menstrual period. In one case a negative test was obtained on the 32nd day, and a positive one 21 days later. Contrary to the experience of Wiltberger and Miller, positive tests were obtained from women on the delivery table—catheterized specimens removed immediately prepartum. In two instances, positive tests were obtained 3 and 6 days after passage of hydatidiform moles.

Forty-eight negative frog tests were confirmed either by Friedman test, by surgical operation (laparotomy, hysterectomy, or curettage) or by subsequent clinical course. Included is one case, with last menstrual period fifteen days before, suspected of being an ectopic pregnancy, in which both frog and rabbit tests were negative. Curettage showed a late proliferative phase, but with a single focus showing decidua. A second frog test twenty-four days later was again negative; the patient was still amenorrheic, but there were no clinical signs of pregnancy, and this was confirmed by the subsequent clinical course. One case perhaps deserves special comment. On July 16, the frog test was negative, whereas the rabbit test gave a questionable positive reaction. On the morning of July 20, the frog test was repeated and was again negative. A hysterectomy performed that afternoon showed no evidence of pregnancy.

There remain to be discussed eleven false negative tests. Three of these represent pregnancies, probably too early to give a positive reaction. One was a young woman whose last menstrual period was on March 28; the frog test was negative on April 29; a repeat on May 20 was positive. The second case was in a 40-year-old woman with a very irregular menstrual history. Her last menstrual period was said to have been on March 23. A frog test on July 16 was negative; a simultaneously performed rabbit test was probably positive. A rabbit test said to have been performed one week before, had been reported as negative. A repeat frog test ten days later was positive. The third case was that of a woman whose last menstrual period had been on June 25; the negative frog test was made on August 4, at which time the Friedman test was positive. A repeat frog test with urine collected on August 9 gave a weak positive reaction. Spermatozoa were found only in a single sample of urine, entrapped in a bit of mucus.

One case occurred in a young woman who brought her first urine three days after she missed her first period. She had a regular twenty-eight day cycle. Four days later, and seventeen days after that, repeat frog tests were run, which both were again negative. A rabbit test performed at the time of the last test was positive. Four days later another frog test was negative; two days later a spontaneous abortion occurred.

There were two cases of negative frog test with positive rabbit test in which abortion occurred. One of these was a tubal abortion in which practically all the chorionic tissue had been destroyed by hemorrhage. Operation was done two days after the frog test. The abortion consisted of mostly necrotic placental tissue.

In one patient with last menstrual period on May 28, on whom a positive frog test was confirmed by a positive rabbit test, performed on August 3, a repeat was done on August 9

TOLERANCE TRIAL OF NEOSTIGMINE METHYLSULFATE IN PREGNANCY

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CONSIDERABLE controversy exists regarding the possible dangers arising from the use of neostigmine in the pregnant surgical patient and for the diagnosis of pregnancy. The present study was undertaken for the following purposes: (1) to determine whether neostigmine methylsulfate* has any effect on the course of pregnancy when administered to gravid women at various stages of gestation; and (2) whether the drug exerts any deleterious effect when used early in pregnancy as a diagnostic aid.

Method

Four groups of patients were picked at random from the clinic of the Boston Lying-in Hospital. The first group, numbering twenty cases, was composed of women in the seventh through the fourteenth week of pregnancy. These patients received 2 c.c. of 1:2,000 neostigmine methylsulfate intramuscularly for three successive days. This is the dosage schedule as outlined for the pregnancy test.¹ The first injection was given as the patient was visiting the prenatal clinic, and the second and third injections were administered at home.

The second, third, and fourth groups were composed of ten patients in the fourteenth through twenty-seventh week, twenty in the twenty-eighth through thirty-fifth week, and twenty in the thirty-sixth week through delivery. The latter three groups were not necessarily normal gravid patients, since their availability as subjects was because they had been admitted to the hospital for various medical conditions. The only patients specifically excluded in this study were those showing signs of vaginal bleeding where there was a possibility of threatened abortion, premature separation of the normally implanted placenta, or placenta previa. The majority of these patients in the latter three groups received 1 c.c. of 1:2,000 neostigmine methylsulfate intramuscularly at intervals of three hours for six successive doses, constituting a total of 3 mg. in fifteen hours.

The first group of twenty cases had seven patients who showed no subjective symptoms or objective signs following neostigmine on three successive days. Seven patients experienced minimal subjective symptoms after either their first or second dose. None had any objective signs, i.e., change in blood pressure or pulse rate. Subjective symptoms included slight dizziness, headache, nausea and vomiting, salivation, and diarrhea. Following each of the two injections, four patients showed the same symptoms of slightly greater intensity. Thick tongue and difficulty of speech of a transient nature were noted in two cases.

One patient, who had diabetes mellitus, complained of slight gagging sensation after the second injection, and flatulence following the third. Another patient received two injections following which she began to bleed.

*Neostigmine methylsulfate used in this study was supplied by Hoffman-LaRoche, Inc.

It has not been determined as yet if the test can be used for quantitative determination of gonadotropin. It may well be that the cyclic change in the seminiferous tubules introduces a variable which would make quantitative results not possible, except perhaps in the winter months.

Summary

The successful use of the male common leopard frog, *Rana pipiens*, in a test for pregnancy, as described by Wiltberger and Miller, and Robbins and Parker, is confirmed.

A modification of the method is described. This modification eliminates the killing of numerous frogs by "toxic" urines, which was early found a serious drawback to the performance of the test as originally described.

The test is reliable (no false positives), although some false negatives were found. The test may be used in summer as well as winter months, though it may prove necessary to use more frogs for each test in the summer, to allow for individual variation in reactivity.

The test is inexpensive, and is sufficiently rapid to be of great value in clinical emergencies, as originally predicted by Robbins and Parker.

It is sufficiently simple so that it may be used even in the smallest laboratories without special equipment, or provision for care of animals.

Acknowledgments: Mr. Saul Saffler gave much help in the preparation of urines and the handling of the animals. I want to thank the several obstetricians and gynecologists who supplied urines from their private practices.

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did not produce any noteworthy subjective symptoms or objective signs of an alarming nature. Forty patients have been delivered of thirty-three infants who are living and well. Two infants died following delivery. There were four stillbirths, one a twin. Two patients underwent therapeutic abortion. Ten patients remain undelivered.

Conclusions

(1) Neostigmine methylsulfate can be safely used in the nonbleeding pregnant patient. (2) When used in early pregnancy as a diagnostic aid, the drug does not interfere with normal gestation, but produced distressing signs in one patient.

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The biological test for pregnancy was positive. She was admitted to the hospital where a vaginal examination under ether anesthesia indicated a normal pregnancy. There was no apparent cause for bleeding. On questioning, it was learned that three weeks previously she had received three daily injections from her family doctor which had resulted in vaginal bleeding on the fourth day. Her pregnancy continued and she was delivered normally at term. Fifteen patients of this group have been delivered of sixteen infants who are living and well. Five patients are still undelivered with apparently normal pregnancies.

The second group of ten cases had eight patients who showed no subjective symptoms or objective signs. One patient experienced nausea and vomiting and headache following the first or second injection, and a second had an exacerbation of an existing headache after three injections. Three patients of this group have been delivered. Two of the infants are living and well. The third was a sensitized Rh-negative patient. She was delivered of a stillborn fetus, death being due to erythroblastosis of the hydrops type. Two patients have undergone therapeutic abortion. Five are undelivered, three of these pregnancies being complicated by hypertension and albuminuria of a mild character.

The third group of twenty cases had twelve patients who had no subjective symptoms or objective signs. Seven patients had symptoms of varying intensity such as nausea, headache, warm flushing, dizziness, frequency, abdominal cramps and gas. None of these symptoms were of any magnitude, the most prolonged being thirty minutes while the majority were more transitory. In one of the three patients complaining of abdominal cramps there was the possibility that these were uterine in origin. One patient had no symptoms, but stained a minute quantity of blood on voiding after the third injection. None had any objective signs. Fifteen patients in this group had been delivered of twelve infants who are living and well. Two infants died, one of marked prematurity. The other died of atelectasis for no apparent cause. There was one stillbirth resulting from toxic separation of the placenta which occurred eight days following the neostigmine tolerance test. Five patients are undelivered.

In the fourth group of twenty cases, twelve patients showed no symptoms. Two of this group had objective signs with one showing slight staining following her third injection, and one patient with ruptured membranes but no labor, showing a rise in blood pressure following the first three injections. Three patients who were at term went into labor during the course of injections. Minimal signs were experienced in four cases, and one patient was uncooperative necessitating withdrawal of the drug after four injections. Twenty women have been delivered with nineteen infants living and well. There were two stillbirths, one a twin from a sensitized Rh negative mother, the other from a mother with severe pre-eclampsia. All of these patients in this group represented either major or minor obstetric problems.

Summary

Seventy patients in various stages of pregnancy ranging from the seventh week through delivery received intramuscular injections of neostigmine methylsulfate. Twenty patients in the first trimester received 2 c.c. of 1:2,000 on three successive days. There was no interference with normal gestation, and fifteen patients have been delivered of sixteen infants who are living and well. The five patients remaining undelivered are following normal prenatal courses.

Fifty patients from the fourteenth week through delivery received 1 c.c. of 1:2,000 neostigmine methylsulfate every three hours for six doses. The drug

most certainly reversible, since in all the reported recovered cases, the blindness and retinal changes disappeared completely. We were most interested in the sharp retinal reversals which occurred in the case to be reported and which incidentally paralleled marked general physical changes.

Treatment

It is generally recognized that the only hope these patients have for survival is prompt termination of the pregnancy as soon as retinal hemorrhage is recognized. Ballantyne has emphasized that the varying impairment of the visual fields which precedes gross hemorrhage may aid in determining an earlier and more opportune time for interruption before the patient is in extremis. Heroic supportive measures to establish a more normal blood chemistry are necessary before operative interference is attempted.

Case Report

Mrs E. M., a 34-year-old, white, gravida ii, para i, was first seen by us in consultation, June 20, 1946. Family history was negative. Past history was not unusual except for an episode of vomiting of three weeks' duration following a normal pregnancy and delivery eleven years previously. This attack of vomiting ceased spontaneously and undiagnosed. History of present illness indicated an amenorrhea since April 19, 1946. Present pregnancy was uneventful until May 28, 1946, when she began to vomit daily. Vomiting followed no particular pattern, had no relation to eating, was accompanied by nausea, and occurred as often as every half-hour. She had received classical but inadequate treatment for approximately two weeks without improvement. Physical examination revealed an adult female in advanced state of dehydration, partially comatose, with temperature of 98.6 F., pulse of 90 per minute, respiratory rate of 20 per minute, and blood pressure 130/70. Salient physical findings were those of an intrauterine pregnancy of 10 to 12 weeks' duration with moderate myofibrosis uteri, and advanced diffuse hemorrhagic retinitis obscuring the disc and vessels. The blood count revealed 9.1 Gm. of hemoglobin and 4,000,000 red blood cells. The patient's blood was type A, Rh positive. A Friedman test had been reported positive. A diagnosis was made of hyperemesis gravidarum, severe, with retinal hemorrhage complicating intrauterine pregnancy. Interruption of the pregnancy was advised as soon as the severe malnutrition and dehydration could be combatted.

A vein was cannulized and, in the next twenty-four hours, the patient received 6,500 c.c. of fluids intravenously, consisting of 1,000 c.c. of sixth molar sodium lactate, 5,000 c.c. of 10 per cent glucose in normal saline solution, and 500 c.c. of whole blood. Sodium Luminal, Gm. 0.3, was administered parenterally in divided doses. On the following day the patient was somewhat improved clinically. Ophthalmoscopic examination revealed that, except for slight peripheral congestion, the diffuse hemorrhagic retinitis of the previous day had cleared. The optic discs were visualized and appeared normal. Normal arteriovenous ratio existed. No pinch crossings and no tortuosity of the vessels were noted. In view of the clinical improvement and with the establishment of relatively normal blood and urine chemistry, it was decided to postpone surgery for another twenty four hours in an effort to improve further the operative risk. By the next morning, June 22, 1946, it became clear that the optimal time for surgery had passed. The patient was again comatose, retinal hemorrhage reappeared as before, the pulse rate rose to 96, and the blood pressure reached 140/80. Under sodium Pentothal and oxygen, with concurrent infusion of whole blood and plasma, the uterus was emptied of a grossly normal ten-week fetus and secundines by dilatation and evacuation. The patient was so comatose that only 0.15 Gm. of sodium Pentothal were required. Intravenous therapy was continued for the next forty-eight hours. The most noteworthy fact in this regard was the administration, over a twenty-four hour period, of 34 Gm. of sodium chloride. Even this amount failed to increase the blood chloride level. Nothing by mouth was permitted during this period. Then followed a gradual transition to full diet. One other transfusion of 500 c.c. of whole blood

HYPEREMESIS GRAVIDARUM WITH RETINAL HEMORRHAGE*

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THE standard textbooks and medical literature exhibit a paucity of information regarding hemorrhagic retinitis in severe vomiting of pregnancy. It is the purpose of this paper to add one typical case to the literature and to emphasize that the high mortality associated with this condition can be lowered only by earlier recognition and proper treatment. Moreover, it may serve to stress further Stander's plea for routine examination of the eyegrounds in the early, as well as the late, toxemias of pregnancy.

Since the first reported case by Erisman in 1890, Stander, Ballantyne, and others have brought the total reported cases to eleven, of which eight were fatal. This case brings the total to twelve, with a mortality of seventy-five per cent.

Etiology

The consensus of opinion is that a disturbance in the metabolism of the carbohydrate chain leads to dehydration, starvation, and incomplete oxidation of fatty acids. This may be a productive factor in the disease, but it is not clear what etiologic agent initiates the vomiting. More recently, Smith and Smith have clearly demonstrated the presence of a toxin, euglobulin, in patients suffering from pre-eclampsia and eclampsia. Perhaps further research will reveal a similar or identical toxin inherent to the pathogenesis of early, as well as late, toxemia of pregnancy. Such a toxin is a plausible explanation for the pathology and response to termination of the pregnancy.

Symptoms, Signs

The usual progression of events in severe vomiting of pregnancy is vomiting, weight loss, dehydration, blurring of vision, hemorrhages into the retina, sometimes generalized petechial hemorrhages, and death.

The abnormal chemical changes in the blood and urine of these patients are reflections of dehydration, starvation, incomplete oxidation of fatty acids, and tissue destruction. Dieckmann and Crossen report no marked urine changes except decreased chlorides and increased ammonia nitrogen. Peckman, Dieckmann, Crossen, and Schjott-Rivers report the blood changes as a definite increase in nonprotein nitrogen, uric acid, and urea, a decrease in chlorides and little change in the carbon dioxide combining power. The blood sugar does not seem to be greatly changed.

Pathology

The characteristic retinal changes are: frequent occurrence of papilledema, absence of exudates, lack of arteriovenous compression, normal arterioles, flame-shaped hemorrhages on, or adjacent to, the optic disc, and loss of vision out of proportion to the fundal changes. Ballantyne in his report cites four cases, in addition to his own, in support of his thesis that the initial disturbance is a central scotoma and papilledema followed by acute bulbar neuritis with blindness and retinal hemorrhage as the final stage. Whatever these changes, they are

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HEMANGIOENDOTHELIOMA OF THE UTERUS*

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TUMORS of blood vessel origin are believed to arise from previously formed capillaries, somewhat in the same manner as those produced in granulation tissue. The endothelial cells of these capillaries sprout to form solid cords which then become canalized.

Tumors of blood vessel type can be benign or malignant. Benign tumors are called angiomas and may be of capillary, cavernous, or venous type. They are very common, widely distributed throughout the body, occur in all ages, and are histologically characteristic of their type. Malignant tumors are called hemangioendotheliomas. They are quite rare—in occurrence and difficult of diagnosis. As far as we know, only one other case of this type has been reported as having occurred in the uterus.

Mrs. F. G., a 47-year-old white woman, complained that her menstrual periods, which ordinarily occurred regularly every twenty-eight days, were now, during the past two years, occurring every twenty-one to twenty-two days. The periods lasted five days, were of moderate amount and painless. She was gravida iii and para iii (children fourteen to twenty-six).

The past history revealed the occurrence of pneumonia in 1920. In 1932, the appendix was removed and a cystic left ovary was resected.

The vulva and vagina were normal. The cervix was cystic. The uterus was small, anteflexed, and mobile. The left tube and ovary were normal. Right adnexa were firm and fibrotic (scarring). Rectal examination negative.

Urine: pH 6.5, albumin 0, sugar 0, specific gravity 1.020. Microscopically, 0 to 1 white blood cell, 1 to 2 epithelial cells. Pregnancy test: negative. Complete blood count: hemoglobin 14.6 Gm., red blood cells 4,960,000, white blood cells 10,100; neutrophils 71, leucocytes 25, monocytes 3, eosinophiles 1 (filamented 67, nonfilamented 4). Blood sugar: 80 mg. per cent. Blood urea nitrogen: 9 mg. per cent. Blood type: 0.

Sept. 14, 1945, a diagnostic curettage was done and demonstrated the presence of the tumor below described.

Sept. 16, 1945, a total hysterectomy and bilateral salpingo-oophorectomy were done under fractional spinal anesthesia. The organs were small, free in the pelvis, and not bound down by adhesions. The removal was uncomplicated, and the postoperative course uneventful.

Pathologic Report.—The first specimen consisting of endometrial scrapings was unlike anything we had previously encountered. The fragments were large, hard, and pale and where the endometrial surface was visible it was finely nodular. The second specimen, two days later, consisted of uterus, cervix, tubes and ovaries. The uterus measured 9 by 5 cm., the wall 2.5 cm. At the right cornua was a hemorrhagic mass 2.5 by 1.5 cm., a blood cyst within the tumor extended to within 2 mm. of the peritoneum at the fundus. A myoma, the size of a pea, was found in the anterior wall. The lining had been thoroughly curetted.

The tubes and ovaries showed nothing remarkable either grossly or microscopically.

Microscopic examination, uterus: In all, eight pieces were taken for paraffin embedding, four from scrapings, three from the tumor and adjacent muscle, and one from the uterine wall above the internal os. They were stained with hematoxylin and eosin and with

*Presented at a meeting of the Philadelphia Obstetrical Society, Oct. 2, 1947.

was given on June 28, 1946. Normal vision returned slowly over a period of days. The patient was discharged July 5, 1946. At this time and on subsequent follow-up visits, she exhibited no residual ocular or cardio-vascular-renal pathologic findings.

Summary

This case presents the characteristic findings of severe hyperemesis with retinal hemorrhage except that, due to the comatose condition of the patient, visual disturbances could not be evaluated. It also illustrates the common pitfall of allowing temporary improvement to give one a false sense of security. We feel that, had she died, we might have been severely criticized for not interrupting the pregnancy twenty-four hours earlier. We cannot comment on the retrobulbar neuritis and other changes which Ballantyne indicates precede gross hemorrhage, inasmuch as we did not see the patient until retinal hemorrhage had developed. We concur with Stander that the hemorrhage is due to increased capillary permeability, associated with profound physical and chemical changes secondary to dehydration and inanition. These changes are reversible and not associated with permanent ocular or cardio-vascular-renal damage. The etiology remains obscure. Prompt termination of the pregnancy resulted in complete recovery.

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Fig. 2.—Hemangioendothelioma of the uterus showing endometrium replaced by tumor. $\times 100$.

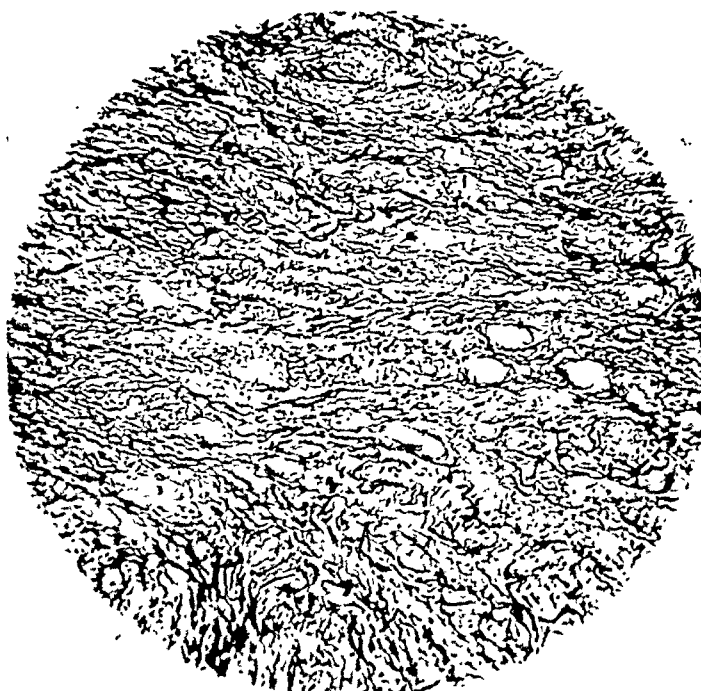


Fig. 3.—Hemangioendothelioma of the uterus showing capillary formation $\times 200$. Foot's reticulum stain.

Foot's reticulin stain. Seven of the sections included what would normally have been endometrium. In only one, that from above the internal os, were occasional endometrial glands found. Everywhere else, the endometrium was completely replaced by tumor. The tumor consisted of small irregular cells. Many were somewhat elongated, and here and there they could be seen to resemble the endothelial cells of blood vessels. The tumor was traversed by enormous numbers of capillaries lined by endothelial cells which in most places were obviously tumor cells. The cells tended to lie very close together; often the nuclei overlapped toward the lumen, sometimes they were heaped up so as partially or completely to occlude the vessel. Here and there they had a whorled arrangement. Many giant cells consisting of clusters of nuclei were seen. Hemorrhages were numerous.



Fig. 1.—Hemangioendothelioma of uterus showing tumor invading the cornua of the uterus.

The reticulin stain showed characteristic capillary anastomoses which in the hematoxylin and eosin sections were obscured by the tumor cells. The tumor presented a well-marked reticulin framework in all the sections stained.

Diagnosis.—Hemangioendothelioma malignum.

Discussion

The gross and microscopic pictures leave little doubt that we are dealing with a malignant tumor. Stout gives as criteria for malignant hemangioendothelioma: first, the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane; and, second, the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumina to anastomose. Both these criteria are fulfilled in our tumor. Grossly, infiltration of the endometrium was widespread and obvious. Infiltration of muscle was certainly present. We attribute the lack of metastases to the fact that malignant tumors of the uterus, especially of the fundus, tend to metastasize relatively late; and, second, that in this case the uterus was removed before

ABSENCE OF TUBE AND OVARY, CONGENITAL OR ACQUIRED

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THIS patient was operated upon by the writer when in charge of the Gynecological service at a Veterans Administration Hospital, and is reported because it presents an etiological problem not conclusively solved and an unusual operative finding which has not been given much attention in textbooks or the literature.

Congenital abnormalities of the vagina and uterus are not uncommon by contrast with abnormalities of development of the urogenital system and the development of the Müllerian ducts and their subsequent fusion from the caudal portion cephalad, starting at the Müllerian tubercle, will account for the more frequent development of abnormalities in the vagina and uterus. Congenital absence of an ovary is not common,¹ but does occur, as may also accessory ovaries. Embryologically there is little or no reason for absence of a tube to be accompanied by absence of the corresponding ovary, since the ovary develops from the celomic mesothelium and underlying mesoblastic stroma quite apart from the Müllerian duct which arises as a tubular invagination of the cells lining the celom, the orifice of the invagination remaining patent to form the abdominal ostium of the uterine tube.²

Whether the case to be presented is one of congenital absence of the tube and ovary or of later acquired absence due to an inflammatory process is not determined.

History.—The patient, A. P., white, aged 22 years, single, was admitted with a complaint of irregular bleeding and pain in the right lower quadrant for the past one and one-half years. Menarche at 15 years, regular in character, every twenty-eight days, but with a moderate flow for only one day. Metrorrhagia in March and April, 1947.

One and one-half years ago, while on duty in the Womens Army Corps, the patient noticed pain when walking or on exertion. A tentative diagnosis of a cyst of the right ovary was made at an Army Hospital, though opinions differed. She was discharged, unoperated upon, but experienced intermittent pain. Although periods had always been regular but of only one day's duration, she flowed from March 22 for eight days and then irregularly until April 22. While flowing excessively in March and April, 1947, the patient states that she had fever. She has had a white vaginal discharge, nonitching, for the past year.

This patient had an abortion in October, 1946, at the fourth month of gestation. This was followed by peritonitis for which she was treated at home with penicillin and medicines. She was in bed for one month.

Physical Examination.—Vulva negative. Vagina: frothy, yellowish white discharge. Cervix in axis of vagina, erosion of posterior lip, os small. Corpus: 4 cm. in size, dextro-rotated and anterior, normal consistancy, regular outline, limited motion. Adnexa: on the right side there is a diffuse, tender mass, circa 4 to 6 cm., narrower at the cornual end, the ovary cannot be differentiated. Left adnexa: no tubal thickening, ovary small.

Laboratory.—Urinalysis, blood count, bleeding time, coagulation time normal. Sedimentation rate 9 mm. per hour. Blood chemistry normal. Serology negative. Cervical culture and smear showed Döderlein's organism predominating. Urethral culture showed diphtheroids, nonhemolytic *Staphylococcus aureus* and *Coliform bacillus*. *Trichomonas vaginalis* present.

Impression.—(1) Chronic salpingitis or (2) possible ovarian cyst, right.

Operation and Findings.—Under general anesthesia, through a midline incision, the abdomen was opened. The right tube was the site of a chronic salpingitis, manifested chiefly by an enlargement of the ampulla and fimbriated end. The fimbria were closed, and the outer

there had been symptoms attributable to the tumor. The diminished intermenstrual time or shortened cycle cannot be attributed to the presence of a tumor, but rather to a beginning of menopause.

The patient has been examined repeatedly since the operation, and so far, has been found to be in excellent condition. She is active and working regularly without any complaints. The last pelvic examination, done July 25, 1948, showed a normal vulva and vagina. The vault of the vagina was held high; there was no evidence of a prolapse. The uterus, both tubes, and ovaries were absent. No pelvic or rectal pathology was felt.

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Accordingly, we must assume that both tube and ovary sloughed and were absorbed or that both were congenitally absent, and the writer believes sloughing the most likely cause, but the history denies the expected previous severe illness.

The author regrets that a complete urological study was not made to rule out possible congenital urinary anomalies which might have been found if the absence of the tube and ovary were congenital in origin.

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half of the tube was enlarged and nodular, with some fine adhesions to the right ovary, which, however, appeared free of infection and normal. On the left side there was no evidence of ovarian tissue. A small thickening about 1 cm. in length, with a closed blunt end extended from the left cornua and was the only evidence of a left tubal structure. On the floor of the pelvis, anterior to the anterior leaf of the right broad ligament, a hard somewhat yellowish plaque was seen. This measured about 16 mm. by 12 mm. by 3 mm. This was attached to the pelvic peritoneum by a few fine adhesions, and was readily lifted off the peritoneum. The corpus uteri was small, firm in consistency, and regular in outline, infantile in type, 3 to 3½ cm. in length, and the cervix about 4 cm. in length.

A right salpingectomy, panhysterectomy, and appendectomy were performed.

Pathologic Report.—Gross: The specimen consisted of uterus and cervix with the right tube attached. The uterus was small, measuring 7 cm. in length and 4 cm. in maximum diameter. The wall measured 10 mm. in maximum thickness and was lined by a thin layer of pale translucent endometrium. The cervix was not remarkable. The right tube measured 9 cm. in length. The lateral extremity was reflected back and adherent to the ampulla, the tube in this region measuring up to 1 cm. in diameter. The fimbriated end appeared closed, and was covered over by adhesions. In the left cornual region appeared a slight projection of nondescript tissue which had been previously cut through. Also submitted was a flat discoid calcified structure, 20 by 13 by 3 mm. An appendix 7 cm. in length was also submitted and was not remarkable.

Microscopic.—Sections of the uterus disclosed a nonsecretory type of endometrium with regular glandular pattern. The myometrium was of less than normal thickness, but not otherwise remarkable. The endocervix showed a mild chronic inflammatory infiltration. Sections of the right tube displayed thickened, adherent plicae with a diffuse infiltration of lymphocytes, plasma cells, and eosinophiles, involving all the coats of the wall. A similar infiltration was noted in the left cornual region in the stump of tissue seen here grossly. The appendix was patent, and its wall showed mild lymphoid hyperplasia. Sections of the decalcified loose body from the pelvis disclosed a thick hyalin capsule suggesting that the structure represented a lymph node. The enclosed material was granular or amorphous with numerous acicular clefts, indicating the presence of lipids. No other tissues or structures were identifiable. Studies of this material failed to offer a reasonable explanation for absence of the left tube and ovary. The loose body appeared to be a calcified lymph node rather than an ovary or a lithopedion which had been considered.

Diagnosis.—Chronic salpingitis, hypoplasia of the uterus, follicular type endometrium, chronic endocervicitis, chronic lymphoid appendicitis, calcified lymph node (tuberculous?).

Comment.—The previous surgical removal of the left ovary and outer portions of the left tube is ruled out by the fact that this patient had not been operated upon either per abdomen or per vaginum if one can exclude the previous abortion which was performed by either a nurse or midwife, was of only a few minutes' duration and performed at home.

The possibility of the absence being accounted for by sloughing of the ovary and most of the tube, as a result of an inflammatory process, cannot at present be denied and seems not too unlikely, though the history gives no indication of a previous severe salpingoophoritis. That this patient had a salpingitis prior to her abortion is obvious, but close questioning gave the impression that it was not of great severity and was misdiagnosed while in the Army as a small ovarian cyst—scarcely a likely mistake if the infection were severe enough to cause sloughing—furthermore the symptoms and findings at all times were purely right-sided. Now considering the possibility that the sloughing occurred post abortal, we must note that the "peritonitis" was not severe enough to require hospitalization, and the patient insisted that during this illness her pain was entirely right-sided.

The hypoplasia of the uterus which was definitely infantile in type, the cervical portion being longer than the corpus, casts a shadow on the diagnosis of a previous pregnancy.

At the time of operation and when examined grossly by the pathologist, it was thought that the calcified plaque was a calcified ovary, but tissue examination did not bear this out.

It was decided to deliver the patient at once by section through a low classical incision. It was thought that this would be the best approach from which to enlarge a uterine incision should the unusual size, shape, or position of the fetus so require. Fortunately this was not the case. The abdominal head was delivered with ease, the pelvic head followed readily, as did the rather broad torso, all with a minimal amount of manipulation. The placenta detached spontaneously and the patient's convalescence was optimal.



Fig. 1.—Uniumbilical-dibrachi-dicephalic monster immediately post partum. Death ensued within the hour.

The monster lived for about an hour, dying just as an electrocardiogram was being attempted. Autopsy was allowed.

Autopsy Findings.—The body was that of a robust male infant with two well-shaped heads and necks set on a single pair of somewhat broad shoulders. The duplication began pectorally, the superior skeletal abnormality being a V-shaped bone which seemed to be fused from scapular anlage. Clavicals were not found.

Two well differentiated vertebral columns continued down to the sacra and were held together, at each rib-level, by a small mutual rib joining the two vertebra so that a large thoracic cage was formed by the lateral ribs of each side and the bridging element.

The duplication was even more remarkable internally. The anatomic structures normally found in the throat and the superior mediastina were present and duplicated. The thymus in

UNIUMBILICAL-DIBRACHI-DICEPHALIC MONSTER; ROENTGENOGRAPHIC DIAGNOSIS IN UTERO, DELIVERY BY LOW CLASSICAL CESAREAN SECTION*

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ORDINARILY the delivery of a monster is not of sufficient interest to warrant report. However, we have not been able to locate any other instance of the diagnosis of a monster of this type in utero and of its subsequent delivery by section under circumstances so favorable for the mother. Indeed certain authorities, notably DeLee, say that this has never taken place.

The usual sequence of events in this obstetric dilemma is for the diagnosis to be entertained only when labor has been long in progress, and the second stage does not develop as expected. After such exposure to exhaustion and to manipulation, it is not surprising that operative procedures, whether destruction or cesarean, are attended with high maternal mortality.

We feel that the sensational aspects of this problem are less important than the practical problem of diagnosis of monsters, the delivery of which by the vaginal route is obviously fraught with the gravest maternal consequences. A careful search of the usual sources has revealed no other instance in which a full-term monster of the uniumbilical-dibrachi-dicephalic type has been diagnosed by prophylactic roentgenography while yet in utero so that cesarean section might be truly elective in every sense of the word.

We wish also to emphasize the relatively atraumatic experience this patient has had, as compared with other cases reported in the literature. Her surgical risk was minimal and her psychic trauma does not seem to have been great enough to discourage her from trying to become pregnant again.

History.—Mrs. J. O., a white married primiparous female, was first seen (J. D'A.) on March 1, 1947. Her history and her physical findings were consistent with those of a two months' pregnancy.

Prenatal findings continued to be entirely normal until about three weeks before the expected date of confinement. At that time abdominal palpation suggested the diagnosis of a twin pregnancy. Two masses, the size and consistency of which suggested (in a parous woman near term) that they were heads, were clearly made out. One was at the pelvic inlet in a position consistent with the last month of pregnancy, the other, apparently of equal size, was in the lower left quadrant, somewhat out towards the flank.

The patient was then referred for roentgen studies. The radiologist (C. M. L.) made the startling diagnosis of a dicephalic monster on the basis of extensive studies. At the time (Sept. 8, 1947) he commented: "Examination of the abdomen in the anteroposterior and lateral projections reveals a twin pregnancy, in the third trimester, one fetal head overlying the pelvic fossa and the other close by in the midabdomen. Because of the unusually close approximation of the fetal vertebral columns, particularly in the lower dorsal, lumbar and sacral areas, right and left posterior oblique exposures were then made. These bear out the constant close approximation of the vertebral columns, revealing only one fetal pelvis, one pair of lower extremities and one pair of upper extremities.

"The maternal pelvis of the gynecoid type and normal in appearance.

"*Conclusion:* Radiologically viable twin pregnancy conjoined from thoracolumbar region distally to a single pelvis."

(The other organ systems were investigated but were in no way remarkable.)

Extreme care was taken to spare the mother reference to a "two-headed monster" and to keep the whole episode as emotionally flat for her as was possible. She has later been able to accept a frank statement about the nature of the infant born to her; that she had "twins which were joined at the trunk" and which had not survived.

Summary

A primiparous white female was thought to have a twin pregnancy. Roentgenographic studies revealed the presence of conjoined twins which were delivered by elective low-classical cesarean section. The monster lived but an hour. The mother's convalescence was not remarkable.

While only of remote value in obstetric diagnosis, this case report illustrates the value of roentgen studies in all cases in which any deviation from the usual is suspected. We consider these studies to be particularly indicated before decision for elective cesarean section is definitely made.

We are indebted to Dr. Charles R. Kingsley, Jr., for advice and suggestions and to Dr. Madeline Penke, Pathologist, who performed the necropsy.

each neck was normal, but displaced laterally somewhat. Equal duplication ceased at the level of the stomachs. The right esophagus emptied into a small stomach situated below and behind the large single liver. The left esophagus and a left stomach were of the type usually seen. The pylora of the stomachs gave onto a double-barrelled duodenum and jejunum, the right element being somewhat smaller and less well defined. The duplication of the ileum was more distinct, each having a small mesentery split off the attachment to the posterior abdominal wall. The cecal-anal bowel was single and not remarkable.



Fig. 2.—Postmortem roentgenogram.

In the thorax each trachea connected with a complete set of lungs crowded into its respective side of the cage. There were two hearts. One, sinistrad, was not remarkable except perhaps that the aortic arch arising from it was somewhat thinner than usual. The pulmonic artery went to the left set of lungs. The second "heart" was dextrad, bilocular, about the size and shape of that of a domestic fowl. From its apex it was attached by a nonpatent fibrous cord to the right auricle of the left heart. From its auricular aspect arose a delicate aorta, the arch of which was poorly defined and the pulmonary artery of which was directed towards the right set of lungs.

The liver was single, perhaps somewhat large, but remarkable only for the presence of two gall bladders and two biliary duct systems, each of which led to its respective duodenum. The pancreas was duplicated, that associated anatomically with the right stomach was somewhat smaller.

At autopsy twin boy No. 1 (C. G. H. Path. No. 46-198) weighed 1,680 grams. There was complete atelectasis of the posterior and basal portions of both lungs, with scattered atelectatic areas throughout the remainder. The brain weighed 210 Gm., and showed vascular congestion of the white matter mainly in the parietal lobes, and hemorrhagic infiltration of the choroid plexus. Microscopically there were large atelectatic areas, and areas of emphysema, in the lungs. The brain and spinal cord revealed no evidence of poliomyelitis, but did show degenerative anoxic changes of the nerve cells of the cerebral gray matter, particularly in the thalamus, with multiple petechial hemorrhages in the cerebral white matter. The pathologic causes of death were prematurity and atelectasis.

Twin boy No. 2 (C. G. H. Path No. 46-188) weighed 1,660 grams. Cyanosis of the body surfaces was pronounced. There were subepicardial hemorrhages around the great vessels at the base of the heart. The brain showed meningeal hyperemia. Microscopically there were small epicardial hemorrhages which reached into the myocardium. Most of the lung alveoli were unexpanded, although some were partially dilated with fluid, blood, and numerous epithelial cells. Bronchioles contained similar material. There was no microscopic evidence of inflammatory alteration of the brain or spinal cord due to poliomyelitis. Pathologic causes of death were given as prematurity, bilateral atelectasis, and focal hemorrhages into the heart, lungs, kidneys, and thymus.

CASE 2.—(C. G. H. No. 74580) Mrs. L. S., a 23-year-old white gravida iii, para ii, was admitted to Colorado General Hospital on Aug. 21, 1946. Her last menstrual period had occurred in December, 1945. Her admission complaints were of aching in the neck and shoulders of thirty-six hours' duration, and a throbbing headache for twelve hours. There had been some diarrhea for two days, and the patient complained mildly of generalized weakness. She had had two previous term pregnancies with normal deliveries and uneventful puerperia.

Physical examination revealed a well-developed young woman who did not appear to be acutely ill. There was some flatterness of the spinal muscle mass in the thoracic region. Nuchal rigidity was moderate. Deep tendon reflexes were normal. The abdomen was distended by a gravid uterus estimated to contain a fetus of about thirty-four weeks' gestation, in left sacroposterior position, unengaged. The fetal heart tones were loud and regular at 140 per minute in the left lower quadrant.

Pertinent laboratory findings were confined to the spinal fluid which contained 420 cells per cubic millimeter with a differential count of 50 per cent polymorphonuclears and 50 per cent lymphocytes. Spinal fluid chemistry showed 64 milligrams per cent sugar and 55 milligrams per cent protein. Admission diagnoses were: acute anterior poliomyelitis and uterine pregnancy, undelivered.

The patient's hospital course was good for the first forty-eight hours. After this interval she began to show respiratory distress with increased voluntary effort, and beginning cyanosis of the extremities. Respiratory distress increased, and fifty-six hours after admission she was placed in a respirator and given endotracheal oxygen. During the following five days there were no changes in her condition. There was never any evidence of fetal distress on repeated examination. On her seventh hospital day she became critically ill, with fever of 104° F., and periods of coma. She manifested involuntary coarse twitchings of the facial muscles. Pulmonary congestion with basal râles and tracheal rattling developed, and shortly after this, she expired without ever having been removed from the respirator.

Postmortem cesarean section was immediately done using the classical technique. A viable female infant weighing approximately 2,800 Gm. was delivered within thirty seconds after the maternal death. The infant was limp and cyanotic but, with mild stimulation and suction, began to cry lustily. Her condition was quite good, despite occasional spasmodic twitchings of the extremities which appeared eight hours after birth and persisted for the next three days. There was never any evidence of central nervous system disease on repeated examinations. She was kept under observation in the hospital for twenty-five days. On discharge she had gained 1 pound, 2 ounces, and she was taking an evaporated milk formula well. Since then she has been followed in the outpatient clinic, and continues to do well.

POSTMORTEM CESAREAN SECTION AFTER DEATH FROM BULBAR POLIOMYELITIS

Report of Two Cases With Living Infants

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(From the Departments of Obstetrics and Pediatrics, University of Colorado Medical Center)

A STUDY of the literature fails to reveal any report of postmortem cesarean section on pregnant women dying of poliomyelitis. It is the purpose of this paper to present two such cases, both of which produced living children.

Case Reports

CASE 1.—(C. G. H. No. 74385), Mrs. F. C., a 31-year-old, white, gravida viii, para vii, was admitted to Colorado General Hospital on Aug. 8, 1946. Her last menstrual period had occurred in January, 1946. Her admission complaints were of neck pain of two days' duration, and of dull precordial pain for about the same length of time. She had vomited once. There had been numbness and tingling of the left hand for several hours. Seven previous pregnancies and deliveries had all been uneventful. Additional relevant history was that one of her six living children had died of acute anterior poliomyelitis in this hospital nine days before her admission.

On examination she was acutely ill, manifesting extreme dyspnea and marked orthopnea. Her extremities were cold and cyanotic. There was mild nuchal rigidity. There was weakness of the left arm. Respiratory efforts necessitated use of the accessory muscles of respiration. Intrinsic chest musculature moved but slightly. She was unable to swallow, and could not cough. The uterus was gravid, the fetus estimated at thirty-six weeks' gestation in vertex presentation, unengaged. Fetal heart tones were faint and irregular in the right lower quadrant. There seemed to be polyhydramnios.

Admission laboratory studies of significance were confined to the spinal fluid which contained 1,700 cells per cubic millimeter, with a differential count of 75 per cent polymorphonuclears and 25 per cent lymphocytes. There were 75 milligrams per cent sugar and 75 milligrams per cent protein. Admission diagnoses were: acute poliomyelitis with bulbar involvement, and uterine pregnancy, undelivered, near term.

The patient's course was steadily downhill after admission, with increasing cyanosis and more labored respirations despite supportive therapy. Within six and one-half hours after admission she was moribund, and preparations were made for postmortem cesarean section. Without delay after her death a classical section was performed, revealing a twin pregnancy. The first infant was delivered forty-five seconds after death of the mother, and his twin about two seconds later.

Twin boy No. 1, C. G. H. No. 74397, weighed approximately 1,800 Gm., voided immediately after delivery, but did not make any respiratory effort for twenty minutes. During this period postural drainage, mouth to mouth breathing, and suction, were employed. With the continued efforts the infant finally began to breathe by himself. He did very well until the twelfth day of life when he regurgitated a small amount of feeding and became cyanotic. Despite therapy he grew progressively worse and died on his thirteenth day of life.

Twin boy No. 2, C. G. H. No. 74398, weighed approximately 1,500 grams. After delivery he made no respiratory effort despite prolonged resuscitatory attempts, and no heartbeat could ever be heard. During resuscitation excessive amounts of amniotic fluid were drained from his nose and mouth.

Significant pathologic findings in the postmortem examination of the mother (C. G. H. Path. No. 46-189) were in the central nervous system, which showed the typical findings and pathologic changes of acute bulbospinal poliomyelitis. The pathologic diagnoses were poliomyelitis, acute bulbospinal type, myocardial hemorrhages, and edema of the lungs.

CARCINOMA OF BARTHOLIN GLAND DUCT*

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(From the Fairview Hospital)

CARCINOMA of Bartholin's gland is considered so rare that it is usually recognized too late to be successfully treated and the diagnosis is seldom suspected before surgical intervention. Simendinger collected only 38 cases of primary carcinoma of Bartholin's gland and, of these, 29 cases were adenocarcinoma and 9 were squamous-cell carcinoma. The latter presumably arose from the duct. Cosbie found one carcinoma of Bartholin's gland in 57 cases of carcinoma of the vulva and in Taussig's series of 155 vulvar carcinomas, 9 originated in Bartholin's gland.

Most authors agree that early metastases to inguinal lymph glands occur and recurrence is common, with poor prognosis in all carcinomas of Bartholin's gland.

The majority of cases occurred between the ages of 40 and 55. There is a divergence of opinion as to whether or not infection is a predisposing factor. Simendinger and Hoffman did not consider it to be a factor, while Taussig, in his later report, found that infection was definitely present in four of nine Bartholin gland carcinomas.



Fig. 1.—Carcinoma of Bartholin gland duct, showing area of multilayered transitional epithelium.

Patient, aged 57 years, noticed a swelling in the lower right side of the vagina for the past year. There was no open ulcer, no bleeding, and no discharge. Examination of the abdomen was negative except for vague tenderness in the right lower quadrant. One deep femoral gland could be palpated on the right side. No perirectal glands were palpable.

The tumor, which was the size of a walnut, was located in the right Bartholin gland and was markedly adherent to the surrounding tissues.

Local excision of the tumor was performed in February, 1945. On histologic examination, one finds striated muscle of the bulbus cavernosus in the surrounding tissue. Many irregular-shaped heaps of multilayered transitional epithelium are present in the tumor.

*Presented at the meeting of the Minnesota Society of Obstetrics and Gynecology at Duluth, Minn., May, 1946.

Postmortem pathologic studies on the mother of this infant (C. G. H. Path No. 46-206) revealed no gross findings of note other than the operative incision. Microscopic examination showed edema of the trachea with infiltration of polymorphonuclear leucocytes and lymphocytes. The lungs contained much fluid, and foci of alveoli were filled with erythrocytes, neutrocytes, and monocytes. An incidental finding was slight edema of the appendix with polymorphonuclear and lymphocyte infiltration. The brain showed diffuse focal areas of infiltration, especially about the dentate nucleus, with perivascular infiltration and small hemorrhages. In the pons these same changes were noted and, in addition, glial proliferation, glitter cells, and early softening were seen. The nuclei of the vagus and hypoglossal nerves were involved, as were the basal ganglia. In the cerebellum perivascular infiltration and microglia were prominent. There was hyperemia of the cerebrum with infiltration of polymorphonuclears, lymphocytes, plasma cells, and considerable glial reaction. Pathologic diagnoses were: Acute anterior poliomyelitis, bulbospinal type, subacute tracheobronchitis, and subacute appendicitis. Sections of the lumbar and cervical cord from this patient were reported as positive for the presence of the poliomyelitis virus.

Comment

Our experience confirms the findings of McGoogan³ and Grelland,⁴ since none of our three infants showed evidence of intrauterine transmission of poliomyelitis from mother to infant.

There is little doubt that the loss of the second twin in the first case in our series was due to intrauterine asphyxia with aspiration of amniotic fluid because of the prolonged period of respiratory embarrassment in the mother prior to her death. The successful result in the second case must have been due to adequate oxygenation of the mother up to the moment of her death. It is interesting to note in retrospect that the fetus in utero in no way interfered with the use of the respirator, nor did the respirator appear to have any untoward effect on the infant.

The poliomyelitis epidemic in Colorado in 1946 showed that pregnancy is no protection against poliomyelitis, and, in fact, it revealed that pregnant women were twice as susceptible to the disease as their nonpregnant sisters.⁵ During the same epidemic the mortality rate in patients in the last trimester of pregnancy with acquired poliomyelitis was 50 per cent.⁵ Should another epidemic of such proportion arise it will be valuable to know that it is possible to save some babies that would otherwise perish.

We wish to acknowledge our indebtedness to the various members of the Department of Pathology of the University of Colorado Medical Center for their assistance in the pathologic reports included in this paper.

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PROLONGED PREMATURE RUPTURE OF MEMBRANES

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PREMATURE rupture of the membranes occurring several weeks before the onset of labor is infrequent. Whenever it is suspected the observer must evaluate the probable site and completeness of the opening in the amniotic sac and the possible influence on continuation of the pregnancy. As a general rule the lower the site of rupture the more abrupt and copious is the fluid escape—in the higher ruptures there is usually a “dribbling” of fluid, containing small flakes of sebaceous material. It is in this latter type that both the diagnosis and prognosis are more difficult and uncertain. In a few such instances the opening in the amniotic sac will heal, and the duration of pregnancy will be unaffected. In most cases labor will ensue at varying periods. We present a case report of proved premature rupture of the membranes, thirteen weeks before labor and delivery.

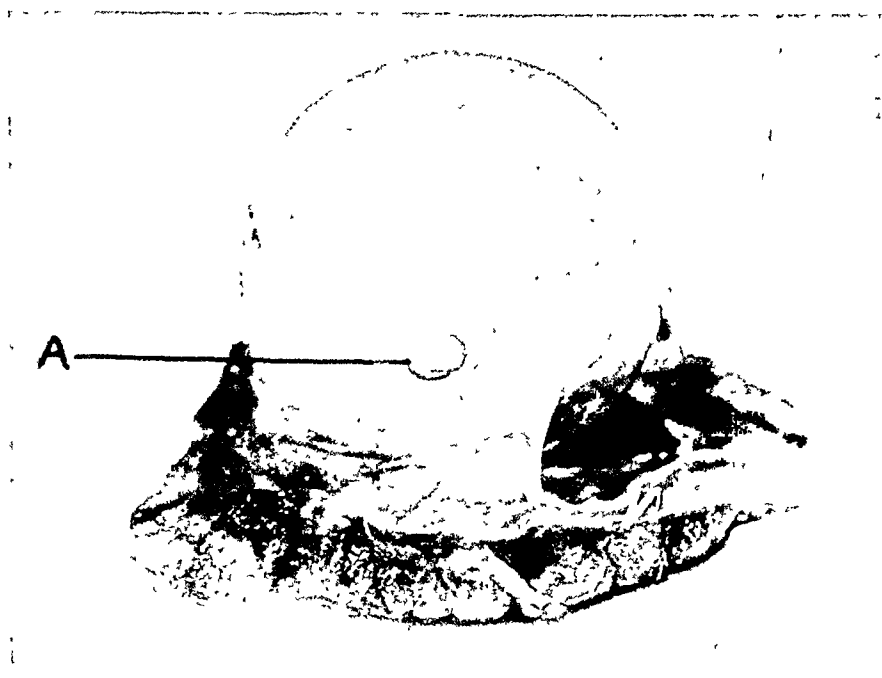


Fig. 1.—A. Site of rupture in the amniotic sac.

M. M., aged 28 years, white, gravida i. Her last menstrual period began Dec. 24, 1944; the estimated date of confinement was Oct. 1, 1945.

When first seen May 4, 1945, physical examination denoted a normal healthy woman with intrauterine gravidity of sixteen to seventeen weeks' duration. Fetal heart sounds were not audible.

On May 7 a sudden gush of clear fluid escaped from the vagina, followed by several similar emissions within the next twenty-four hours. There was no pain or bleeding. The patient was given 30 mg. of Pranone orally daily in an attempt to render the uterus less irritable. During the subsequent twenty-four hours of observation no further fluid was seen. The uterus was not irritable, and fetal heart sounds were distinctly audible. The cervix was uneffaced and undilated. Pranone therapy and bed rest, except for bathroom privileges, were advised. Tub baths, douches, and intercourse were forbidden.

The nuclei are irregular and, for the most part, are oblong in shape. There is no adenomatous pattern in any portion of the specimen. One does not see any normal structure of Bartholin's gland or its duct. (The late Dr. Robert Meyer who reviewed the slides felt that there was no question that the tumor was a carcinoma of the duct of Bartholin's gland.)

A few days after local excision, a radical vulvectomy with excision of the superficial and deep inguinal glands on both sides was done, with removal of a part of the vagina above the tumor. On examination, the glands showed inflammatory reaction.

In November, 1945, the patient returned with a local recurrence in the posterior fourchette on the right side, which was excised and showed carcinoma of the same type.

The patient was alive in April, 1948, with no local recurrence of the tumor.

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Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

It seems but a short time since I reviewed the fourth edition of Berkeley and Bonney's *A Textbook of Gynaecological Surgery* but upon investigation, I find that five years have elapsed. Now the fifth edition appears by Bonney¹ alone as Sir Comyns Berkeley has died. More than ever the book bears the personal imprint of Bonney, the versatile and distinctive surgeon who has illustrated the volume with his own simple and direct line drawings (590 illustrations). The book is meant for the surgeon who performs gynecological operations only now and then, but has an equal appeal for the gynecologist who wants to refresh his memory on some phase of an operation with which he is well acquainted. Anyone who has watched Bonney's uncanny skill at the operating table, his dexterity and speed, will find some of this individuality within the pages of his book. There may be no particular need for the special instruments and gadgets which the author has invented and uses, such as the vaginal clamp, dissecting forceps, wrist-reel, etc.

Bonney uses Indoe's technique in the inlay grafting operation for absence of the vagina. I agree with Bonney that the Baldwin operation for absent vagina might well be omitted from the next edition. The author advocates an orificial plastic operation for vaginismus (Fenton's). He might have devoted a few words to the selection of cases and the nonoperative treatment which is far more frequently applicable. Various techniques for vesicovaginal fistula operations are described, including transplantation of the ureters into the colon as a last resort. Cervical and intrauterine operations are detailed. I am pleased to note that Bonney favors supravaginal hysterectomy unless there are cogent reasons for removing the cervix, and also abdominal over vaginal hysterectomy. However, both vaginal and abdominal hysterectomy are depicted minutely.

The author's unique experience with the Wertheim operation and his description of this alone would make this book worth while. Another field, in which he has been a pioneer, is that of myomectomy. The chapter on cesarean section is complete.

In anterior colporrhaphy, neither the dissection nor the method of suture takes full cognizance of the anatomical structures; this applies as well to the depiction of the Manchester operation for prolapse. I note with surprise that a patient after a Le Fort operation is kept in bed twenty-one days. As I reserve this operation for the debilitated and aged, my practice is to get them up by the third day! For recurrent cases of stress incontinence of urine, he uses Terence Millin's modification of the Stoeckel-Goebell pro-

¹*A Textbook of Gynaecological Surgery.* By Victor Bonney, M.S., M.D., B.Sc. (Lond.). F.R.C.S. (Eng.), Hon. F.R.A.C.S., Hon. F.R.C.O.G., M.R.C.P. (Lond.). Consulting Gynaecological and Obstetric Surgeon to the Middlesex Hospital; Consulting Surgeon to the Chelsea Hospital for Women; Honorary Consultant on Gynaecology and Obstetrics to the Army; late Visiting Gynaecologist to the British Postgraduate Medical School; late Gynaecological Surgeon to the Royal Masonic Hospital and Queen Alexandra's Hospital, Millbank. Late Member of Council and Vice-President of the Royal College of Surgeons of England. Sometime Member of the Central Midwives Board and Examiner in Diseases of Women and Midwifery to the Conjoint Board of England; Hon. Fellow of the American Gynaecological Society; Hunterian Professor, 1978-38-31, Bradshaw Lecturer, 1934, and Hunterian Orator, 1943, Royal College of Surgeons of England. Formerly Emden Research Scholar Cancer Investigation Laboratories, Middlesex Hospital. Fifth Edition. With 590 original drawings by Victor Bonney and 17 colour plates. 328 pages. Paul B. Hoeber, Inc., New York. 1948.

On May 24 there was a similar sudden gush of fluid and fluid continued to escape in varying amounts, sometimes requiring the use of five pads daily. The fundus measured 19 cm., and the fetal heart sounds were still normal.

Labor began Aug. 15, 1945, and terminated with frank breech decomposition and extraction under pudendal block and nitrous oxide analgesia following left posterolateral episiotomy. The child cried vigorously and was apparently normal in development. It weighed 2,044 Gm.; the length was 38 cm., and the fetal course was uneventful following initial incubation and oxygen therapy. The child on discharge from the hospital was normal, weighing 6 pounds, 8 ounces. The maternal postpartum course was uncomplicated and afebrile.

The placenta measured 15 cm. in diameter. In the amniotic sac approximately 5 cm. from the periphery was a sharply delineated circular opening 1 cm. in diameter. The edges of the opening were smooth and round. Microscopic section of the amniotic sac across the opening showed "the edges to be covered with a membrane similar to the covering of the rest of the sac." (Fig. 1.)

The authors are to be congratulated on this new edition which offers an outstanding study of the problem in both partners in a childless marriage, with complete and detailed instruction for investigation, specifically defined indications for treatment, and for the family doctor a good interpretation of laboratory reports, and help in assessing and improving the constitutional problems involved.

PHILIP F. WILLIAMS.

The third edition of Hunt's *Diseases Affecting the Vulva*,³ appearing within eight years, shows how much appreciated the dermatologic approach has been. Changes have affected therapy mainly. The sulfonamides and penicillin have revolutionized the treatment of venereal disease and are of value in other conditions. Vitamin A is of value in hyperkeratoses; vitamin D in lupus vulgaris; podophyllin in condylomata acuminata. This monograph is of real value and assistance.

R. T. FRANK.

*Gynaecological Histology*⁴ by Josephine Barnes consists mainly of 162 microscopic illustrations beautifully reproduced in black and white, with a commentary text. Both normal and abnormal tissues of the female genital tract such as are seen in gynecological practice are described and shown. Purposely, many rare conditions have been omitted as this is designed for the final year of the medical student. Between the short text and the detailed captions, a large amount of ground is covered. There is only one poor illustration, that is Figure 26, of adenomyosis. The classification of ovarian tumors is simple and adequate. The description of carcinoma of both the body of the uterus and of the cervix is very good. The final chapter deals with pregnancy. This is an admirable, simple laboratory guide which is equally good for both student and teacher.

R. T. FRANK.

*Gynecological and Obstetrical Anatomy*⁵ by Smout, with chapters on the histology and endocrine control of the female by Jacoby, is in its second edition. In addition to a very detailed osteology with description of the pelvic types, the pelvic joints, the pelvic floor, its connective tissue and fasciae, the uterus, tubes, ovaries, and vagina are described both anatomically and histologically. The hormones and their actions are given in detail. The anatomy of prolapse of the genitourinary tract is described. Chapters on the lymphatics, innervation, the fate of the ovum, the placenta, and the anatomy of the fetus insofar as it affects childbirth are included.

There are 185 illustrations including many colored plates and diagrams illuminating the text which is clear, informative, but dry and somewhat monotonous.

R. T. FRANK.

Two authors, Calle and Restrepo, discuss leucorrhea⁶ in three divisions—trichomonas; Donné, casuistic; finally, 700 cases of every variety of leucorrhea including those due to specific organism, presented in a haphazard fashion.

R. T. FRANK.

³*Diseases Affecting the Vulva*. By Elizabeth Hunt, B.A., M.D., Ch.B. (Liverpool). Honorary Consulting Dermatologist, South London Hospital for Women; Honorary Dermatologist, New Sussex Hospital for Women and Children, Brighton; Temporarily Honorary Dermatologist, Royal Infirmary, Liverpool; Formerly Senior Medical Officer, Radium Institute and Hospital for Skin and Cancer Diseases, Liverpool; Acting Honorary Dermatologist, Royal Sussex County Hospital, Brighton. Third Edition, Revised. 211 pages. With 36 illustrations and 19 plates in colour. The C. V. Mosby Company, St. Louis. 1948.

⁴*Gynaecological Histology*. By Josephine Barnes, M.A., D.M. (Oxford), M.R.C.P. (London), F.R.C.S. (England), M.R.C.O.G. assistant, Obstetric Unit, University College Hospital, London; Assistant Obstetrician and Gynaecologist, Elizabeth Garrett Anderson Hospital; Surgeon, Marie Curie Hospital. Member Correspondent, Société Française de Gynécologie. With 162 illustrations. 242 pages. Harvey & Blythe, Ltd., London. 1948.

⁵*Gynaecological and Obstetrical Anatomy*. By C. F. V. Smout, M.D., M.R.C.S., Assistant Professor, Department of Anatomy; Sub-Dean and Tutor, Faculty of Medicine, University of Birmingham. With Chapters on The Histology of the Female Reproductive Tract and Its Endocrine Control. By J. Jacoby, M.D., Ph.D., Lecturer in Histology, Department of Anatomy, University College, Cardiff; formerly, Department of Physiology, University of Birmingham. Second Edition. 218 pages. The Williams & Wilkins Company, Baltimore. 1948.

⁶*Flujos Genitales Femeninos*. By Dr. Alonso Restrepo. Trabajos de la Academia de Medicina de Medellín. Reproducción de "Anales de la Academia de Medicina de Medellín". III Época—Vol. III—No. 2—Julio 1946.

cedure, the entire operation being performed from above. To my surprise, he still uses ventrofixation in some cases of prolapse, and describes two round ligament shortening operations and one of his own.

Space prevents me from giving details on his operations for ovarian cysts, for relief of tubal closure by implantation, and for myoma and pregnancy. There are chapters on intestinal surgery, including on abdomino-vaginal excision of the rectum, drawing the bowel through the split posterior vaginal wall. The concluding chapters deal with post-operative treatment, transfusion, postoperative complications of every variety, the repair of ventral hernia, etc. Little more than mere mention of penicillin is made. Mortality statistics as well as remote sequelae conclude this volume, which is of unusual interest and value as it presents the experience of a master surgeon for more than 36 years.

R. T. FRANK.

In a foreword to this volume on *Sterility and Impaired Fertility*,² Lord Horder stresses the importance of this world-wide problem and refers to the distribution of the etiological factors over many fields of medicine. He suggests that constitutional factors are more important than anatomical factors, and while the problem is one for teamwork, most of the investigation may be done by the family doctor.

In the preparation of this second edition, Lane-Roberts and his co-authors assess the significance and value of much new work in this field, suggest the use and interpretation of postcoital tests, especially the more recent invasion test, the technique of semen analysis, and the determination of pregnandiol in urine. They also add new material in the discussion of cyclical temperature records for the study of ovarian function, and in the use of cytological studies in determining ovarian function.

The opinions expressed in the first edition as to the use of endocrine preparations as therapeutic aids have shown a considerable shift. The use of these hormones is much more precisely defined. The treatment of subclinical infections in the cervix, long recognized as a cause of subfertility, by the sulfonamides and penicillin rather than the cautery or other surgery is mentioned, and much attention is directed toward constitutional treatment in the elimination of toxic conditions. The use of x-ray stimulation, particularly of the pituitary gland, in the treatment of anovulation is also discussed. The authors bring out the legal, moral, and social aspects of artificial insemination by means of donated semen. While they agree that the short term effects may have been good, and that it has been an acceptable solution to many childless marriages, they caution the possible involvement of dysgenic factors.

The text begins with a general survey of the problems and then treats the male factors in childless marriages in five chapters, comprising 162 pages. Chapter Five, on the male reproductive mechanism and its disturbances, offers technical advice for the urologist or andrologist in addition to much material which should aid the family doctor in his part of the problem.

The two chapters concerning sterility in the female, on the investigation of the woman, and on treatment of the lesions which in her may be responsible for the impairment of her reproductive power are thoroughly considered. The authors, in discussing operations to restore tubal patency, say that the probability that a given operation will result in the restoration of fertility is presumably much lower than some given figures suggest. There is an excellent discussion on tubal insufflation.

There are nine appendices to the text and they bring out the technical details of examination of semen, study for pregnandiol, the biologic tests for pregnancy, and the invasion tests, and the study of waking temperature charts, and the technique, and the dangers, of ovarian and pituitary irradiation. There are many fine photomicrographs and roentgenograms among the illustrations.

²*Sterility and Impaired Fertility, Pathogenesis, Investigation and Treatment.* By Cedric Lane-Roberts, C.V.O., M.S., F.R.C.S., F.R.C.O.G., Gynaecological Surgeon, Royal Northern Hospital; Albert Sharman, M.D., Ph.D., M.R.C.O.G., Senior Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow; Kenneth Walker, M.A., M.B., B.C.(CANTAB), F.R.C.S., F.I.C.S., Jacksonian Prizeman and Hunterian Professor, Royal College of Surgeons, Andrologist, Philip Hill Parenthood Clinic; B. P. Wiesner, D.Sc., Ph.D., F.R.S.E., Consulting Biologist, Royal Northern Hospital; Mary Barton, M.B., B.S., First Assistant to the Fertility Clinic, Royal Free Hospital, London. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York and London, 1948.

It is evident that the advances of the past six years have been well evaluated for inclusion in the revised text. On the whole, one feels that the teaching given here is modern, conservative, and easily understood. The section on management and feeding and injuries and diseases of the newborn comprises one-tenth of the subject matter. It is of interest to note that in the assimilation of the literature and the revision of the text there is no bibliography or reference to specific contribution to the literature.

The conciseness and simplicity of presentation and the jointly considered opinions of ten contributors make the text a valuable contribution.

PHILIP F. WILLIAMS.

Dr. O'Donel Browne's *Manual of Practical Obstetrics*⁹ appears in a second edition after a lapse of twelve years, a delay occasioned by the war. This excellent and concisely written manual is intended chiefly for the student and general practitioner and the reviewer feels that the book thoroughly accomplishes the aim of the author. The section on disease of the newborn has been omitted in this volume, but the subject of fetal birth injuries is retained and includes not only specific injuries, but also a short and well-written section on fetal erythroblastosis. The arrangement of the text is logical and the line drawings which are plentiful serve well to amplify the text.

It is apparent that chloroform is still a frequently used anesthetic in labor in England, while the subject of caudal anesthesia is considered in four sentences. A conservative note is struck regarding vaginal operative delivery and it is noted that the illustrations portray application of forceps and delivery in the left lateral as well as the dorsal position. The discussions on puerperal hemorrhage and toxemia show a marked agreement between the practice of the Rotunda Hospital and that of practically any maternity institution in the United States. The classical and the low cervical cesarean sections are well considered; no mention is made of the extraperitoneal technique. The concluding chapter in the book, radiology in obstetrics, by McDonogh, has some well executed roentgenograms. The book is a fine text for students and guide for general practitioners.

PHILIP F. WILLIAMS.

Eden and Holland's *Manual of Obstetrics*¹⁰ has been revised in this ninth edition by Alan Brews. The book has been enlarged by 41 pages, and 40 very excellent x-ray films have been added in addition to over 150 new illustrations. This nearly 800 page book reflects the teachings and practice of obstetrics at the London Hospital and is, therefore, of real interest over here. Every one of the nine parts has been thoroughly revised; particularly, all of the newer improvements in obstetric teaching and therapy which have occurred in the last nine years have been included. Embryology and physiology are given in considerable detail and are very well illustrated. The treatment of hyperemesis and toxemia is about the same as practiced here except that intravenous therapy is not as much emphasized as it might be. In my opinion, curettage for abortion is suggested at too early a stage. The work by American authors on Rh factor, diabetes, toxemia, etc., has been freely and fully incorporated in the text. Rectal examination during active labor deserves more emphasis than it has received. The author agrees that in placenta previa, the modern trend of use of cesarean section is fully justified. While the antibiotics are mentioned and recommended in infection, I find no mention of streptomycin or of the anti-coagulants in the treatment of thrombosis. Obstetric operations are well described and illustrated. The concluding chapter on social care of the patients, which means extra

⁹A *Manual of Practical Obstetrics*. By O'Donel Browne, M.B., M.A.O., M.A., Litt.D., F.R.C.P.I., F.R.C.O.G., Master, Rotunda Hospital, Dublin; King's Professor of Midwifery, Dublin University; Gynaecologist to the Stewart's Hospital, Co. Dublin. Second Edition, 251 pages, with 8 color plates and 218 illustrations, The Williams and Wilkins Co., Baltimore, 1948.

¹⁰Eden and Holland's *Manual of Obstetrics*. Ninth Edition. By Alan Brews, M.D., M.S. (Lond.), M.R.C.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G. Obstetrical and Gynaecological Surgeon, the London Hospital; Director of Obstetric Studies, London Hospital Medical College; Examiner in Midwifery and Diseases of Women, University of Cambridge, the Conjoint Examining Board in England and the Royal College of Obstetricians and Gynaecologists; Late Examiner in Midwifery and Diseases of Women, University of London. With 36 plates, 12 in colour, and 465 illustrations in the text. 796 pages. J. & A. Churchill, Ltd., London. 1948.

Obstetrics

Twenty-two years have elapsed between the first and the seventh, the present, edition of this book.⁷ Certainly it fulfills a useful purpose and must be regarded as having lived up to its title of recent advances. This seventh edition has six new chapters replacing a similar number discarded from the previous edition, and the remainder of the text gives evidence of thorough review of the literature and additions to our knowledge of the two subjects.

The text is characterized by an amplification of the purely physiological details of many of the subjects presented, notably nutrition, weight changes, and water retention in pregnancy, lactation, and hemorrhagic disease of the newborn, and erythroblastosis. The subject of nutrition in pregnancy is amply dealt with and the review of the literature has been critical. The second chapter on weight changes and water retention in pregnancy particularly develops the physiological as well as the pathological influences concerned with this topic. L. J. Davis, of Glasgow, considers anemia of pregnancy under six headings, devoting most of his space to the hypochromic anemias, but giving an excellent discussion of the rarer forms occasionally encountered.

The American literature on caudal anesthesia is reviewed at length. Bourne and Williams feel that it is a method which must be very seriously considered as an addition to our various obstetric analgesics. In a discussion of spinal anesthesia for obstetric surgery, the editors state that it is difficult to avoid the conclusions that this anesthesia is inherently dangerous. The antibiotics are fully discussed in all their applications. The physiological aspects of lactation and recent animal experimentation are given at length to explain the function of lactation in women. Again, in the section on erythroblastosis, the authors devote considerable space to the subject of the Rhesus subgroups and the atypical forms of father, mother, infant reactions.

There are three excellent sections, by Rohan Williams and W. M. Levitt, on radiology in obstetrics, radiological investigation and diagnosis in gynecology, and x-ray therapy in gynecology. The latter two chapters thoroughly supplement an excellent discussion on cancer of the cervix uteri. The physiology and the pathology of the control of urination in the woman is detailed in Chapter Twelve. The anatomico-physiologic mechanism of control is well illustrated and the authors present the technique and illustrations of Aldridge's procedure as well as Millen's sling operation.

The present edition takes stock of the new discoveries and trends in opinion in these two specialties, both as regards the experimental work, and the practical usefulness of new knowledge from the literature of many countries.

PHILIP F. WILLIAMS.

Midwifery, by Ten Teachers under the direction of Clifford White and edited by him, Cook, and Gilliat appears in its eighth edition.⁸ The present contributors and editors form an imposing list of British specialists and teachers. The text has been achieved in a unique manner through having one author revise each section in accordance with the reports and suggestions made to him by the other nine contributors. This cooperation and adjustment of opinions and practice give mediated expression of the present teaching of the subject in the British Isles. The textbook is comparable to the larger volumes by American authors; the subject matter is formally presented in forty-seven chapters, thoroughly illustrated.

⁷**Recent Advances in Obstetrics and Gynaecology.** By Aleck W. Bourne, M.A., M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., Obstetric Surgeon to St. Mary's Hospital; Consulting Obstetric Surgeon, Queen Charlotte's Hospital; and Leslie H. Williams, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G., Obstetric Surgeon to In-Patients, St. Mary's Hospital, Consulting Obstetric Surgeon, Queen Charlotte's Hospital. Seventh Edition, 321 pages with 85 illustrations. The Blakiston Company, Philadelphia, Toronto, 1948.

⁸**Midwifery, By Ten Teachers.** Under the direction of Clifford White, M.D., B.S. (Lond.), F.R.C.P. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G., edited by Clifford White, Frank Cook, and William Gilliat. Eighth Edition, 541 pages with 217 illustrations. The Williams & Wilkins Company, Baltimore, 1948.

Every detail of preparation, instrumentarium, mode of anesthesia, including continuous caudal, intravenous, pudendal, etc., is indicated. The use of the sulfonamides and anti-coagulants is described. Penicillin is reserved for the gravest conditions because of its costliness. The Rh factor is discussed.

Among bloodless dilatation methods, the laminaria or tupelo tent still is described. It is used for dilatation in the third and fourth month; in the fifth he packs the cervix or uses bags. Hebostiotomy is described but has little more than historical interest. Version, correction of malposition, and reposition of prolapsed parts are gone into in great detail with ample illustrations. Forty-eight pages are devoted to breech extraction, with 53 illustrations. The fetal mortality is said to be 10 to 20 per cent. Forceps and their use are covered in even greater detail, with 96 illustrations. The mutilating operations are then taken up. The low flap cesarean, the extraperitoneal technique, and the Porro operations are given with indications. In the large clinics of Spain, cesarean operation was performed in from 1 to 5.7 per cent of births.

Repair of birth passages, treatment of exudates, of breast abscesses, and vaginal hysterectomy are described. This volume is very ample and detailed and covers the entire subject minutely. It is unusually well illustrated and faultlessly gotten up.

R. T. FRANK.

Pathology of Pregnancy comes from the fluent and prolific pen of Raul Briquet,¹⁶ professor at the University of São Paulo, Brazil. It is an exceptionally well gotten up book with 177 illustrations derived from diverse sources to which due credit is accorded. The chapter bibliographies are right up to date (including 1947) and American sources are widely quoted.

The subject is covered thoroughly: the pregnant woman—infections such as syphilis and tuberculosis, the disturbances of various organs and organ systems including endocrinopathies, dermatoses, malformations, local inflammations of the genital tract, and toxicoses including eclampsia; ovarian pathology—ectopic gestation, placenta previa, abortion, abruptio, hydramnios, mole and chorionepithelioma (where I am pleased to note that Marchand's simple classification is adhered to). The concluding chapter deals with sterility. The book covers the subjects concisely but minutely and adequately and contains an immense amount of information, including methods of treatment.

R. T. FRANK.

Fasc. 8 of *Bibliotheca Gynaecologica*, published by S. Karger, now of Basel and New York contains Merz' **Normal and Pathological Physiology of Lactation**.¹⁷ This 36 page monograph takes up the hormonal secretions which activate the glands, the psychic nervous and physical mechanisms which assist during the lactating phase. Factors leading to difficulties or impediments of lactation are analyzed as well as methods of treatment.

R. T. FRANK.

Management in Obstetrics by Claye¹⁸ is designed as an aid for the general practitioner who, though no specialist, is an accoucheur. Abortion, antenatal supervision, diet, vomiting are discussed. Various obstetric conditions, presentations, and complications are dealt with summarily and dogmatically. Except for a few pictures depicting breech extraction, the book lacks adequate illustration. A very elementary and sketchy presentation.

R. T. FRANK.

¹⁶**Patologia da Gestação.** By Professor Raul Briquet, Catedrático de Clínica Obstétrica e Puericultura Neo-Natal. Da Faculdade de Medicina Da Universidade De São Paulo. Com 177 Figuras No Texto. 603 pages Editora Renascença, S.A. São Paulo, Brazil. 1948.

¹⁷**Normale und Pathologische Physiologie der Lactation.** von W. R. Merz. Aus der Universitätsklinik Basel (Direktor Prof. Dr. Th. Koller). 36 pages. *Bibliotheca Gynaecologica, Supplementa ad Gynaecologia.* International Monthly Review of Obstetrics and Gynecology. *Revue Internationale Mensuelle d'obstétrique et de Gynécologie, Monatsschrift für Geburtshilfe und Gynäkologie*, Fasc. 8, Redactores E. Anderes-Zürich, Th. Koller-Basel. S. Karger, Basel. Switzerland, 1948.

¹⁸**Management in Obstetrics.** By Andrew M. Claye, M.D., F.R.C.S., F.R.C.O.G., Professor of Obstetrics and Gynaecology, University of Leeds; Surgeon, Maternity Hospital and Hospital for Women, Leeds; Examiner, Royal College of Obstetricians and Gynaecologists. 166 pages. Geoffrey Cumberlege, Oxford University Press, London. 1948.

rations, maternity benefits, almoner for the care of unmarried pregnant women, applies to the present local conditions in the British Isles.

This is a good book which, with very few changes and additions, would be as popular here as it is abroad.

R. T. FRANK.

A report of the Obstetrical Hospital Cosme Argerich has appeared for 1947.¹¹ This maternity hospital has from 800 to 1,000 confinements a year. The report contains diverse obstetrical topics by members of the staff. It is a nicely prepared and a very presentable volume.

R. T. FRANK.

Pregnancy Diagnosis Tests: A Review¹² by Cowie is an epitome covering the huge bibliography on this subject. As it was published under the auspices of the Commonwealth Agricultural Bureau (Joint Publication No. 13) it deals primarily with veterinary medicine but includes everything on the human being. The author covers seven classes of tests. Among the clinical tests, he mentions the diagnosis in the cow, mare, ewe, goat, sow, and bitch, cat, and rabbit. In the hormonal tests, various animals, mouse, rat, rabbit, guinea pig, male rodents, amphibia, fish, and even plants which are used as indices, are described. Likewise chemical and enzymatic tests are mentioned.

This is a very valuable contribution bringing together under one cover an encyclopedic amount of information. The bibliography is large and universal.

R. T. FRANK.

Discovery of the Rh factor has cast light on erythroblastosis fetalis and some hemolytic reactions following blood transfusion. Under the auspices of the Medical Research Council, Mollison, Mourant, and Race report on the **Rh Blood Groups and Their Clinical Effects**.¹³ They deal with the Rh groups, including classification, application to determination of paternity, ethnographic and genetic basis, and calculation of Rh chromosome frequencies. The clinical effects cover production and detection of sensitization, fetal and neonatal effects, premature termination of pregnancy, treatment of the infant by various types of transfusion, etc. In conclusion, Rh testing—typing of cells, tests for Rh antibodies, matching and special tests and techniques—is described. This is a condensed but complete guide.

R. T. FRANK.

Dowkontt, a plastic surgeon, has written a small book on the **Hygiene of the Breasts**¹⁴ designed for the laity. He describes diets for overweight, brassieres for the adolescent, exercises and postures, care during pregnancy. He approves of breast nursing. Diseases, especially cancer and inflammation, are touched upon. Exercises to beautify, hormone creams to develop, operations to reduce, and the corsetière are discussed.

R. T. FRANK.

Lorca's **Textbook on Obstetric Operations**¹⁵ is one of the few Spanish books received by us. It is a large, nearly 700 page, tome with 509 illustrations which, the author emphasizes, are one and all original. They are well executed with lavish use of two colors.

¹¹*Anales Del Servicio de Obstetricia del Hospital Cosme Argerich. Año 1—Vol. 1.* Director Prof. Dr. Juan Leon; Secretario de Radacion Dr. Nino Castelberg. Direccion Hospital Cosme Argerich, Almirante Brown Y Py Margall. 203 pages. Buenos Aires. 1947.

¹²*Pregnancy Diagnosis Tests: A Review.* By Alfred T. Cowie, B.Sc., M.R.C.V.S., Ph.D., National Institute for Research in Dairying, University of Reading. Commonwealth Agricultural Bureaux Joint Publication No. 13. 283 pages Commonwealth Bureaux of Animal Breeding and Genetics, Edinburgh; Dairy Science, Shinfield; Animal Health, Weybridge. Great Britain. 1948.

¹³*The Rh Blood Groups and Their Clinical Effects.* By P. L. Mollison, A. E. Mourant and R. R. Race. Privy Council Medical Research Council Memorandum No. 19. 74 pages. London: His Majesty's Stationery Office, 1948.

¹⁴*The Hygiene of the Breasts.* By Clifford F. Dowkontt, M.D. 222 pages. Emerson Books, Inc., New York. 1948.

¹⁵*Tratado Practico de Operaciones Obstetricas.* Por el Dr. Carlos Lorca, De la Cruz Roja Española (Madrid) (Ex Profesor axiliar de Obstetricia y Ginecología en la Universidad Central; antiguo becario de la Junta Constructores de la Ciudad Universitaria de Madrid; laureado por la Sociedad Ginecologica Española, etc.). Con 509 figuras, totalmente originales, en negro y color. 697 pages. Editorial Científico-Médica, Madrid-Barcelona, Spain. 1948.

Our present techniques do not allow us to differentiate tinctorially the various secretory elements developed by glands. The experimental embryological work on *organizers* and *evocators* in embryologic development, the corticomedullary inductors which determine sex in the bisexual anlage are of fascinating interest as are the phyto hormones of plants.

It is impossible to continue a detailed description of the immense amount of material contained, which covers the usually described internal secretory glands but from a broader viewpoint. In dealing with the pancreas, the gastrointestinal principles are fully described; with the adrenal gland, a very full description of the emergency theory, of the effects on metabolism are taken up. The approach is interesting and in many ways novel. The illustrations are numerous, many of them original delicate line drawings. The book contains a mine of information presented in a fascinating way. Between its covers one finds integrated studies which have appeared in widely scattered departments of research.

R. T. FRANK.

Number 79-80 of the "Spanish Collection of Medical Monographs" is a 68 page brochure by Bishop of London, translated into Spanish by Cañadell on **Gynecological Endocrinology**²³ for the general practitioner.

In addition, there are six shorter articles on diverse topics, four by Spanish authors, one by an English author, and one by an American.

R. T. FRANK.

Miscellaneous

Recent Advances in Surgery by Edwards,²⁴ with "The Thorax" by Brock, "The Nervous System" by Northfield, and "Radiotherapy in Malignant Disease" by Sir Stanford Cade, is in its third edition. It contains a large amount of accurate and up-to-date information in small compass including all major advances. The American literature is utilized fully.

Information on the electrolyte balance, antibacterial and anticoagulant therapy are included. In addition to thorax and nervous system, the alimentary tract, the blood vessels and the ductless glands are dealt with.

The text is clear and direct, the illustrations numerous, the bibliography adequate. This is an excellent book from which to obtain recent advances quickly and adequately.

R. T. FRANK.

The third edition of Smith and Gault's **Essentials of Pathology**²⁵ in the same large format with double column of text and 740 illustrations appears after six years. General and systemic pathology with the aim of emphasizing practical and essential factors is featured. Parasitic infestations and cancer, because of their increasing importance, are emphasized. The case histories, 261 in number, roentgenograms and pictures, integrate pathology with clinical subjects, add interest, and give the book a real and broad value rarely attained by the classical books of pathology. The ample and excellent illustrations form a veritable atlas. The short chapter bibliographies are carefully selected. This book is both instructive and interesting.

R. T. FRANK.

²³**Endocrinología Ginecológica para el medico general.** Por P. M. F. Bishop, D.M. (Oxon.) Profesor de Fisiología aplicada de la Escuela de Medicina del Hospital Guy, Endocrinólogo del Hospital Guy, Endocrinólogo del Hospital de Mujeres de Chelsea. Versión española por el Dr. J. M. Cañadell, Del Departamento de Endocrinología de la Clínica Médica B (Facultad de Medicina de Barcelona). 68 pages. Colección Española de Monografías Médicas. Administración: Ediciones B.Y.P. Barcelona. 1948.

²⁴**Recent Advances in Surgery.** By Harold C. Edwards, C.B.E., M.S., F.R.C.S., Surgeon and Lecturer in Surgery, King's College Hospital, London. Surgeon to the Evelina Hospital for Sick Children. Dean of the Medical School, King's College Hospital, Late Consulting Surgeon, Central Mediterranean Forces. Third Edition. With 131 Illustrations. 437 pages. The Blakiston Company, Philadelphia. 1948.

²⁵**Essentials of Pathology.** By Lawrence W. Smith, M.D., F.C.A.P., formerly Professor of Pathology, Temple University School of Medicine, Associate Professor of Pathology, Cornell University Medical School, and Assistant Professor of Pathology, Harvard Medical College. Corresponding Member of the Royal Flemish Medical Academy of Belgium; and Edwin S. Gault, M.D., F.C.A.P., Associate Professor of Pathology and Bacteriology, Temple University School of Medicine. With a foreword by the late James Ewing, M.D., Memorial Hospital, New York City. Third Edition. 764 pages. The Blakiston Company, Philadelphia and Toronto. 1948.

Since 1935 Vignes has published a series of monographs on *The Diseases of the Pregnant Woman*. The present brochure entitled *Eclampsie et Eclampsisme*¹⁹ is the seventh. It is a fully documented and exhaustive exposition covering every aspect and containing a minute scrutiny of the world's literature.

R. T. FRANK.

Reproduction and Survival by R. Christie Brown²⁰ postulates that "reproduction aims at the survival and variation of the race but that the individuals participating are mere pawns in the game." Some parents escape lightly, like some of the fishes, others run a hazard but "nature always takes more care of Life than she does of lives." Evolution, selection, survival of the fittest, asexual and sexual reproduction are discussed briefly but clearly. The evolution from the sea, to fresh water, then to the land is marked by the change from careless and simple breeding (oyster, fishes) to complicated reproduction and parenthood.

Primitive reproduction is wasteful. More advanced breeding reduces the number of eggs, increases their size and affords better protection (carried in mouth, in pouch, placenta and uterus). The hormones of reproduction, estrogen and progesterin are described. Along these same lines, evolution, reaction of the embryo to its environment, labor as an instrument of natural selection and allied topics are dealt with. This little book is well worth while and pleasurable reading.

R. T. FRANK.

Volume XXXII of *Contributions to Embryology*²¹ contains six articles. Corner (No. 207) discusses alkaline phosphatase in the ovarian follicle and corpus luteum, using six species including the human being. Speert (No. 208) describes the normal and experimental development of the mammary gland of the rhesus monkey. Development, cyclical changes, ablation experiments, pregnancy effects, lactation, etc., were studied. Estrogens, progesterone, androgen and desoxycorticosterone acetate all produced mammary development. Witschi (No. 209) studied the migration of the germ cells of the human embryo from the yolk sac, through the hind gut, mesentery into the mesonephric fold, into the gonadal fold by means of their own active movement. Gillman (No. 210) deals with the development of the gonads in man, the role of the fetal endocrines and the histogenesis of ovarian tumors. Streeter (No. 211) gives a third survey of the "Developmental Horizons in Human Embryos," covering four age groups and their organ development, with amazingly fine detail drawings by Didusch. The final article by Doreas Padgett describes the development of the cranial arteries in the human embryo.

R. T. FRANK.

Endocrinology

Turner's *General Endocrinology*,²² written by a zoologist, is designed less for the medical student, who, however, can obtain much useful information from it, than for the student of biology, the approach being experimental rather than clinical. The author emphasizes that endocrinology should be viewed "as a branch of physiology which deals with the chemical integration of the organism and embraces much more than the conventional ductless glands." Whether, for example, the kidneys should be regarded as an endocrine gland (because of the renin—hypertensinogen-tension mechanism) is a matter of opinion. The "milieu intérieur" and the importance of tissue fluids are emphasized.

¹⁹*Eclampsie et Eclampsisme*. Par Henri Vignes. 217 pages. Maladies Des Femmes Endocrites. Masson et Cie, Paris, VI^e, France, 1948.

²⁰*Reproduction and Survival*. By R. Christie Brown, M.D., M.S., F.R.C.S., F.R.C.O.G., Obstetric Surgeon, City of London Maternity Hospital; Hon. Surgeon Samaritan Free Hospital for Women; Gynaecologist, Metropolitan Hospital. 168 pages. Edward Arnold & Co., London. 1948.

²¹*Contributions to Embryology*. Volume XXXII, Nos. 207 to 212. 261 pages. Carnegie Institution of Washington Publication 575, Washington, D. C. 1948.

²²*General Endocrinology*. By C. Donnell Turner, Ph.D., Associate Professor of Zoology at Northwestern University, Chicago. Illustrated, 604 pages. W. B. Saunders Company, Philadelphia and London. 1948.

In discussing asphyxia of the newborn, both antenatal and postnatal, the author refers to the large part this plays in the mortality of the newborn on the first day of life. The causes of asphyxia before delivery are enumerated, and the influence of anesthetic and analgesic agents is stressed. The disturbances of the placental circulation are mentioned, and stress is laid on the importance of recognition of intrauterine anoxia, pointing out the significance of both sudden drops and persistent slowing of the fetal heart beat. He suggests the therapeutic use under these circumstances during labor of oxygen administration to the mother.

The pathology of asphyxia is well described and the author discusses mouth-to-mouth insufflation, inhalation of 5 per cent carbon dioxide and oxygen, and the use of pure oxygen. Infants who finally breathe with any measure are best protected by incubation and 50 per cent oxygen atmosphere for some time after birth. The value of drug treatment of apnea is questioned. The author discusses the mechanics used for resuscitation.

The methods of physiologic therapy, including the apparatus for inhalation therapy, the use of pressure and administration of aerosols, is thoroughly gone into, and the techniques of many types of instruments fully explained. While the volume will be particularly interesting to those dealing with acute and chronic respiratory disease, it should also be of great help to divisions of anesthesiology which today in many hospitals are intimately concerned in the administration of these methods of physiologic therapy.

PHILIP F. WILLIAMS.

The three-volume **Clinical Laboratory Methods and Diagnosis**²⁸ in its fourth edition is an increasingly ambitious attempt to cover all phases of laboratory technique with concise interpretations. It succeeds fairly well in 3,103 pages. The good handiwork of co-authors improves particularly the partially revised sections on bacteriology, protein metabolism and parenteral protein hydrolysate therapy, toxicology and police crime methods, optical crystallography, parasitology and tropical medicine, Rh factor, antibiotics and their assay, and electrocardiography.

Up-to-date laboratory information is presented relative to antibiotics, salmonella organisms, virus diseases in general, atypical pneumonia, influenza, vaginal smears, and toxicologic problems. Improvement in procedures such as "blood-phenol level" and "protein-bound iodine," although not as yet universally used, should have been noted.

A very useful portion of the material is an accurate compilation of techniques selected from personal experience, personal communications, and from the literature. Unfortunately, a good many of the techniques, terms, and references to the literature are principally of only historic interest. Further, there is an unfortunate introduction of commercialism by the tendency to show undue preference for equipment and reagents of certain manufacturers, instead of naming several or all interested firms.

The subject matter is well organized and clearly presented. Many intricate facts and theories are simply and logically explained to furnish an easy and adequate working knowledge for the uninitiated. However, the author lapses into the history of an isolated case all too frequently to illustrate a point. Of note are certain ambiguous statements, e.g., the inaccurate suggestion that splenectomy is ordinarily useful in leucemia. Nevertheless, there are many minute pearls (such as "short cuts" in technique) available to a semi-experienced and wary physician or technologist. One attraction to this set of books is the fact that there is nearly always available a procedure which yields an answer useful to the clinician.

Most illustrations are good, e.g., vaginal and bronchial smears, smears of nasal secretion, and the pictures of colorimetric reactions. The hematologic color plates are fair. Many of the old illustrations are poor and their legends do not state the degree of magnification. The index is well organized and complete.

²⁸**Clinical Laboratory Methods and Diagnosis.** By R. B. H. Gradwohl, M.D., D.Sc., F.R.S.T.M. and H. (London), Director of the Gradwohl Laboratories and Gradwohl School of Laboratory Technique; Pathologist to Christian Hospital; Director, Research Laboratory, St. Louis Metropolitan Police Department, St. Louis, Missouri. Fourth Edition. Volumes I and II, 2284 pages, with 691 illustrations and 51 plates. Volume III, separately indexed, 819 pages, with 420 illustrations and 7 plates. The C. V. Mosby Company, St. Louis, 1948.

In this book, *The Mechanism of Abdominal Pain*, Dr. Kinsella²⁶ suggests that mechanism for splanchnic pain does not differ essentially from that for somatic pain. He states that the underlying factors, anatomic and physiologic, are identical as are also the effective painful stimuli, whether physical (experiment) or pathological. After briefly reviewing the various conceptions of abdominal pain, the text proceeds to describe in detail the three pathways, bulbar, thoracolumbar, and sacral, which carry the nerve impulses from the abdominal viscera to the central nervous system.

Various succeeding chapters take up visceral sense, referred pain, cutaneous reactions, tenderness and rigidity, adhesions, and the various sections of the alimentary tract. In Chapter fifteen the author refers to the pain of appendicitis as having two components, the visceral and the parietal, and the origin and pathways of these impulses are discussed, repeating to a certain degree the previous analysis (Chapter Six) of cutaneous hyperalgesia in appendicitis. He notes the atypical distribution of pain in the normally placed appendix as well as in the abnormally situated organ, and refers to the importance of the psoas ridge in promoting the remarkable constancy of McBurney's point.

He raises three points of interest regarding pain arising in the uterus and adnexa: the persistence of pain during labor following presacral neurectomy; again, the pain produced by palpation of an inflamed ovary in the pouch of Douglass, especially when overlain by a retroverted uterus. He considers this an expression of direct visceral tenderness since parietal peritoneum does not lie between the affected viscus and the examining finger; and finally, that the pain produced on grasping an inflamed cervix with a vulsellum proves that the apparent insensitivity of the viscera is only relative; that visceral pain may arise not only direct by disordered motor activity, but also through inflammation. In the final chapter he sums up his reasons for belief in direct visceral tenderness as well as for direct visceral pain, concisely summarizing his theories and the proofs as he has found them.

PHILIP F. WILLIAMS.

The aim of the book, *Physiologic Therapy in Respiratory Diseases*, by Dr. Barach,²⁷ as in an earlier text by him on inhalation therapy, is to bring out the principles and practices of physiologic therapy in respiratory disease. The therapeutic use of gas and other measures which have a specific value in counteracting clinical disorders of breathing are discussed. The pathologic physiology of each clinical entity is explained, as well as the physiologically based procedures by which it may be combated. The subject of practical techniques in current use has been thoroughly considered. After a short section on the historical background of the topic, there is an extended presentation on anoxia. This is followed by a concise chapter on each of the various etiologic lesions and their therapy.

Of interest to gynecologists and obstetricians should be the chapters on massive collapse of the lungs and postoperative atelectasis. Seventy per cent of the former follow surgical operation and injury. The treatment recommended is inhalation of from 5 to 7 per cent carbon dioxide and oxygen to stretch the bronchial walls by maximum expansion of the chest in hope of freeing the usual mucous plug, and having it subsequently coughed up. Inhalation of from 50 to 70 per cent oxygen is regarded as useful as generally indicated in the maintenance of respiratory function before and after the carbon dioxide therapy. The author discusses the effect of anesthetic agents and the reduction of vital capacity by the abdomen in producing postoperative atelectasis. The preoperative use of penicillin and hyperventilation is mentioned as well as bronchoscopy, intubation, and aspiration.

²⁶*The Mechanism of Abdominal Pain*. By V. J. Kinsella, M.B., Ch.M. (Syd.), F.R.C.S., (Eng.), F.R.A.C.S., Hon. Surgeon, St. Vincent's Hospital, Sydney, Hon. Surgeon, Hornsby Hospital. 210 pages and 17 illustrations, Australasian Medical Publishing Company Limited, Sydney, 1948.

²⁷*Physiologic Therapy in Respiratory Diseases*, by Alvan L. Barach, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital New York, N. Y. Second Edition. 396 pages with 74 illustrations. J. B. Lippincott Company, Philadelphia, London, Montreal, 1948.

Correspondence

Irradiation in the Treatment of Amenorrhea and Sterility

To the Editor:

When irradiation was suggested for the treatment of amenorrhea and sterility many years ago, it met with a great deal of adverse criticism because of the supposed possibility of injury to the children born of irradiated mothers. This criticism continued with increased furor up to the present time when the effects on animals were utilized to prognosticate the abnormal effects that might be expected in human beings following irradiation of their reproductive organs.

In 1928, I reported in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* my first series of cases treated by x-ray therapy and stated, "When properly treated no harm ensues to the patient or to her offspring" Since that time, over the course of twenty-five years, I have treated several hundred women for sterility, with the birth of more than 150 children perfectly normal in every way. Several reports of this work have been published from time to time.

However, what of the children of these children born of irradiated mothers? No one as yet had reported on this third generation. Again, based only on animal observations, dire calamities were predicted for the children of those born of irradiated mothers.

I warned against accepting this prognostication, but of course had to wait until the children of irradiated mothers matured and married and reproduced. I am now ready to report on a third generation baby. This baby boy was born on Oct. 25, 1948, to a young woman who was born to an irradiated mother in January, 1927. This baby boy is entirely normal and is the first third generation child born of irradiated mothers.

The history in this case is as follows:

Mrs. H. A. was referred to me, by Dr. I. C. Rubin, on June 9, 1925, for amenorrhea, dysmenorrhea, and sterility. She was 28 years of age. Menstruation began at 11 and was never regular. She married at 26 and continued to have irregular, painful periods and had not been able to conceive. Her last period was on May 3, 1925.

She received a course of x-ray therapy to the ovaries in the prescribed manner between June 9 and June 30, 1925. Following treatment, the patient menstruated regularly for nine months without pain, became pregnant, and in January, 1927, gave birth to a normal baby girl.

This baby girl matured normally, menstruated regularly beginning at the age of 13. She was married on March 4, 1946. Contraceptives were used until last year. She became pregnant and now, on Oct. 25, 1948, gave birth to a perfectly normal baby boy, weighing 6 pounds at birth.

I feel warranted, therefore, in reiterating my previously published conclusions that irradiation, when properly given, is harmful neither to the mother nor to the offspring and that it has proved a valuable therapeutic procedure for the treatment of amenorrhea and the relief of sterility.

Because my original report was published in this *JOURNAL* and because I should like to bring this successful conclusion to the attention of the profession so that they may now employ this method in the treatment of sterility without fear of abnormal consequences, this letter brings the data on this subject up to date.

JRA I. KAPLAN, M.D.

755 PARK AVENUE,
NEW YORK.
Oct. 30, 1948.

Volumes I and II may be purchased as a unit and are most useful to the laboratory of the small hospital where economy is necessary and where experts in the subdivisions of the laboratory are not available. Volume III is a very well illustrated, fairly complete treatise on parasitology and tropical medicine which may be purchased separately, if desired. It is written with the coauthorship of Dr. Pedro Kouri, Director of the Institute of Tropical Medicine and Professor of Parasitology and Tropical Medicine in Havana University.

PHILIP F. WILLIAMS.

The second Index Volume of Surgery, Gynecology & Obstetrics,²⁹ recently issued, constitutes a valuable and comprehensive presentation for ready reference of the contents of this important periodical publication for a period of twenty years from July, 1925, to July, 1945. The wealth of material contained in its 750 pages, effectively indexed and cross indexed, provides an adequate bibliographic survey of these fields of medicine. The book is recommended as an admirable work of reference.

GEO. W. KOSMAK.

Item

Fellowship Announcement

A Fellowship in obstetric and gynecologic endocrinology will be available at the Jefferson Medical College and Hospital on or about May 1, 1949, under the direction of Dr. A. E. Rakoff, Assistant Professor of Obstetrics and Gynecology, and Endocrinologist to the Department of Clinical Laboratories.

The Fellowship is available to Doctors of Medicine who have had at least one year or its equivalent of postgraduate training in obstetrics and gynecology. Applicants for the Fellowship should communicate at once with Dr. Lewis C. Scheffey, Professor of Obstetrics and Gynecology, Head of Department, and Director of Division of Gynecology, Jefferson Medical College and Hospital, Philadelphia 7, Pa.

²⁹Index, Surgery, Gynecology & Obstetrics, Volumes 41-80, 1925-1945. Editor, Loyal Davis, Associate Editors, Sumner L. Koch, Michael L. Mason, Assistant Editor, M. E. Spencer. Published by the Franklin H. Martin Memorial Foundation, 24 East Erie Street, Chicago, Illinois.

Openers of Discussion:

1. Dr. F. S. Parkes (London).
2. Dr. S. Bender (Liverpool).

Invited Speakers:

1. Dr. P. M. F. Bishop (London).
2. Dr. C. Crooke (Birmingham).

8:45 P.M. Reception by the President and Council of the Royal College of Obstetricians and Gynaecologists at the University of London, Bloomsbury, W.C.1.

THURSDAY, JULY 7, 1949.

Morning Session. 10 A.M. Chairman: Sir William Gilliatt.

“Essential Hypertension in Pregnancy”

Introduced by:

1. Professor George W. Pickering (London).
2. Professor F. J. Browne (London).

Openers of Discussion:

1. Mr. G. F. Gibberd (London).
2. Mr. A. Dickson Wright (London).

Invited Speaker: Professor R. J. Kellar (Edinburgh).

Afternoon Session. 2 P.M. Chairman: Dr. John Hewitt.

(1) “The Management of Pregnancy in Diabetics.”

Introduced by:

1. Mr. John H. Peel (London).
2. Dr. G. Douglas Matthew (Edinburgh).

Opener of Discussion:

1. Dr. W. G. Oakley (London).
- (2) “Hernia of Pouch of Douglas.”

Introduced by: Mr. Charles D. Read (London).

Openers of Discussion:

1. Mr. A. A. Gemmell (Liverpool).
2. Mr. Alexander C. Palmer (London).

Invited Speaker:

1. Mr. C. M. Gwillim (London).

8-10:30 P.M. Reception by the President of the Congress at the Zoological Gardens by courtesy of the Council of the Zoological Society of London.

FRIDAY, JULY 8, 1949.

Morning Session. 10 A.M. Chairman: Professor O'Donel T. D. Browne.

“Modern Concepts in Diagnosis, Treatment and Prognosis of Carcinoma of the Uterus.”

- (1) “The Diagnosis by Vaginal Smear.” Dr. J. E. Ayre (Montreal).
- (2) “Precancerous Cellular Changes in Carcinoma of the Cervix.” Professor Gilbert I. Strachan (Cardiff).
- (3) “Prognosis Based on Biopsies.” Mr. A. Glucksmann (Cambridge).
- (4) “The Operation of Pelvic Exenteration.” Dr. Joe Meigs (Boston, Mass.).

A discussion will follow each paper.

Afternoon Session. 2 P.M. Chairman: Dr. E. Chalmers Fahmy.

Discussion on Maternal Mortality.

Introduced by: Sir William Gilliatt.

Openers of Discussion:

1. Professor Dugald Baird (Aberdeen).
2. Mr. Percy Stocks (Leeds).
3. Sir Eardley Holland (London).

Invited Speakers:

1. Dr. G. W. Theobald (Leeds).
2. Dr. H. R. MacLennan (Glasgow).

7:45 P.M. Congress Banquet in Guildhall.

For further information apply to the secretary, Mr. A. Joseph Wrigley, 58 Queen Anne Street, London, W. 1.

Items

International and Fourth American Congress on Obstetrics and Gynecology

May 14 to 19, 1950, Hotel Statler, New York City

Further plans for holding this international gathering have recently been announced by the sponsoring group, the American Committee on Maternal Welfare.

The preliminary program for the scientific sessions, as developed by the General Program Committee of which Dr. Howard C. Taylor, Jr., of New York is the chairman, is as follows: The morning meetings, Monday through Friday, May 15 to 19, are general sessions each devoted to one of five topics, (1) physiology of human reproduction, (2) the pathology of human reproduction, (3) social and economic problems, (4) neoplastic diseases of the female reproductive system, and (5) obstetric and gynecologic procedures.

The afternoons will be given over to meetings of various groups represented at the Congress, including nurses, nurse-midwives, hospital administrators, educators, practicing physicians, investigators in special fields, and public health doctors and nurses. Arrangements for these meetings are under the direction of the following committees: medical section, Dr. Newell W. Philpott, Montreal, Quebec; educators and investigators, Dr. George W. Corner, Baltimore, Maryland; hospital administrators, Dr. G. Otis Whitecotton, Oakland, California; public health, Dr. Edwin F. Daily, Washington, D. C.; and nurses and nurse-midwives, Miss Margaret A. Losty, R.N., of New York City.

The technical exhibit is under the direction of a special committee of which Dr. Woodard D. Beacham of New Orleans is chairman. Dr. John Parks of Washington, D. C., heads the committee in charge of the scientific exhibit. The committee in charge of arranging the motion picture program is under the direction of Dr. Archibald D. Campbell of Montreal. Applications for space in the scientific exhibit or for time on the motion picture program should be submitted to the chairmen in charge of these activities on official application blanks obtainable from the business office of the International Congress at 24 West Ohio Street, Chicago 10, Illinois.

All inquiries pertaining to the meeting should be addressed to the Chairman of the International and Fourth American Congress on Obstetrics and Gynecology, Dr. Fred L. Adair, at 24 West Ohio Street, Chicago 10, Illinois.

The Twelfth British Congress of Obstetrics and Gynaecology

July 6, 7, 8, 1949, London, England

Program of Proceedings

WEDNESDAY, JULY 6, 1949.

Morning Session. 10 A.M. Chairman: The President, Sir Eardley Holland.

The Congress will be declared open by the Minister of Health.

“Modern Caesarean Section”

Introduced by Mr. C. McIntosh Marshall (Liverpool).

Openers of Discussion:

1. Mr. A. W. Purdie (London).

2. Dr. Bécélère (Paris).

Invited Speakers:

1. Dr. Ninian Falkiner (Dublin).

2. Mr. Frank Stabler (Newcastle).

Afternoon Session. 2 P.M. Chairman: Professor Hilda Lloyd.

(1) Guest Paper, “Endometriosis,” Dr. Joe Meigs (Boston, Mass.).

(2) “The Methods of Assay and Clinical Significance of Pregnanediol in the Urine.”

Introduced by:

1. Professor C. F. Marrian (Edinburgh).

2. Dr. G. I. M. Swyer (London).

The reactions with which we are concerned in this report are those incurred during radium and roentgen treatment of the pelvis in cases of cervical cancer. For this condition, radium application is usually confined to the uterine canal and upper vagina. The sphere of its activity is comparatively limited; yet, in addition to the uterus and cervix proper and the upper vagina, the bladder and rectum may be affected, as may even the small bowel if it happens to be adherent to the uterus. However, the *volume* of tissue affected is small so that significant primary reaction to radium irradiation is rare. The local reaction, true, may be intense. Roentgen therapy for cervical cancer is usually delivered through relatively large skin fields, usually two anterior and two posterior, approximately 10 by 15 cm. each. Occasionally, lateral fields, over the hips are employed, and still less frequently, only two large fields are used, one to cover the lower abdomen anteriorly and one to cover the back. All of these techniques necessitate the passage of the x-rays through large epithelial surfaces, large volumes of muscle and supporting connective tissues and fasciae, some portions of both small and large bowel, and bone. A certain amount of this is inevitable if the x-rays are to reach the tissues at which they are aimed, i.e., the parametria and the regional pelvic lymph nodes. With the combination of the two sources of irradiation, then, there are many possibilities for harm. Indeed, there have been enough very distressing and not infrequently fatal complications in our series of cases to warrant analysis. It seems no triumph to us to cure the cancer at the expense of making a "radiation cripple" of the patient. We feel certain that a comparable situation must exist wherever similar techniques have been employed.^{3, 4, 5, 7, 11, 12}

Before going on to the actual analysis, a brief discussion of the specific reactions will help to clarify the problem. Immediate reactions have to do with the cytolytic effects of radiation and the alterations in body metabolism which result from breakdown products; or they are related to the lighting up of infection as a result of the radiation procedures.^{2, 4} Since *radium* irradiation affects a relatively small volume of tissue, general effects are comparatively rare and usually insignificant. In a small proportion of cases nausea may be experienced. Not infrequently there is a febrile reaction, sometimes incident to the packing with transitory occlusion of drainage and sometimes due to infection. The actual placing of radium in these patients often involves strenuous manipulation of a seminecrotic, infected cervix so that infection may be spread to the adjacent parametrium and lymphatics. Occasionally, serious generalized infection results. It is doubtful if irradiation per se lights up infection; it may be that the manipulations incident to the placement of radium cause the trouble. On the other hand, *roentgen* therapy affects a large volume of tissue so that immediate general effects are more common. This is associated with considerable dermatitis, dermatolysis, and mucositis involving the epithelium of both bowel and bladder.^{1, 10} "Radiation sickness,"¹³ which may occur even before destructive tissue effects can take place, is sometimes seen. Its true nature is unknown. However, the composite result of the "radiation sickness" and the cytolytic effects may be anorexia, nausea, vomiting, often diarrhea, urgency and frequency of urination, and a certain amount of prostration. Occasionally a patient is "overwhelmed" and dies.

The *late* tissue effects of radiation have to do principally with changes in the connective tissues; these are chiefly proliferative.² This involves thickening of blood vessel walls with narrowing of vessel lumina, and thus diminution in

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Original Communications

REACTIONS TO X-RAY AND RADIUM THERAPY IN THE TREATMENT OF CANCER OF THE UTERINE CERVIX

DANIEL G. MORTON, M.D., AND JOHN A. KERNER, M.D., SAN FRANCISCO, CALIF.

(From the Department of Obstetrics and Gynecology, University of California Medical School)

THE reactions of the human organism as a whole and of individual tissues as entities to irradiation as available by radium and by high voltage roentgen rays are of great importance, since, at the present time, irradiation is either the treatment of choice or the only treatment possible for a large variety of malignant tumors. It is well known that malignant tumors are more susceptible to the gamma rays of radium and x-rays than are normal tissues. Indeed, it is upon the basis of this differential effect that the use of irradiation for malignant disease depends. Theoretically, it should be possible to destroy *any* malignant tumor by irradiation if one could arrange to deliver a sufficient amount to all parts of the tumor. From a practical point of view, this is often not possible because of the limiting effect of the surrounding normal tissues. Not infrequently, in an effort to deliver a lethal dose of irradiation to the tumor, surrounding normal tissues are overirradiated, producing a variety of unfortunate effects which vary from those of minor degree to such marked tissue alterations that death of the patient may follow. The radiation therapist is constantly seeking to raise his dose level to efficient proportions without overirradiating normal tissues. On the other hand, another puzzling variable which adds to the difficulty of determining the proper dose is that of irradiation sensitivity. The same amount of irradiation does not produce identical tissue reactions in all individuals.

Reactions of normal tissues to irradiation may be divided in several ways: as immediate or late; or with reference to the particular tissue or tissues affected; or according to whether the reaction is of mild or severe degree. The latter depends largely upon the volume of tissue irradiated and the dose; the greater the volume of tissue exposed and the greater the dose, the more severe is the reaction likely to be. Reactions also depend upon the character of the tissue irradiated: i.e., whether it is bowel, bladder, spleen, liver, lung, or a combination of different organs. Some of the tissues are much more susceptible than are others.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

monly associated with cervical necrosis, sections of which frequently showed no viable cancer cells); acute pelvic inflammatory disease; acute pyelonephritis; pelvic thrombophlebitis; extensive pelvic peritonitis; severe radiation reaction of the rectum with ulceration. In most of these instances the temperature was rather markedly elevated. These severe immediate reactions were sometimes followed by prolonged illness or even death. For example: A patient developed a pelvic abscess which eroded into a major vessel causing death from hemorrhage. One patient developed a severe pelvic inflammatory disease which did not respond to therapy, and the patient eventually died of sepsis. Another patient developed colitis and diverticulitis; eventually one of the diverticuli ruptured. Still another patient had a severe rectal reaction with bloody diarrhea; eventually she developed proctitis and a rectal stricture with partial obstruction. Under *moderate* immediate reactions have been included: instances of parametritis, cystitis, pyelonephritis, proctitis, peritonitis, enteritis, colitis, and cervical necrosis associated with fever of moderate degree, e.g., temperature of 37.5° C. to 38° C. for two consecutive days, excluding the first postoperative day, and often involving a prolonged hospital stay with low-grade fever. Whenever the febrile reaction was slight or did not appear at all, the reaction was classified as *mild*.

Of the 580 patients who received radium therapy either alone or in combination with x-ray 2.6 per cent had severe reactions, 6.9 per cent moderate reactions, and 90.5 per cent mild reactions. Table I represents an attempt to correlate the degree of immediate reaction to radium with the dose given. Interestingly, no significant differences could be determined when the dose was considered in this manner nor was a difference noted when the group which received radium alone was compared with the group which received both radium and x-ray therapy. (However, at times, radium therapy was stopped temporarily or reduced because of severe reaction. This would increase the number of severe reactions with lower doses of radium in this table.)

TABLE I. RADIUM THERAPY: REACTIONS

DOSE	NUMBER OF PATIENTS	SEVERE		MODERATE		MILD AND NONE
		NO.	PER CENT	NO.	PER CENT	
Less than 4,000 mg.hr. radium alone	85	3	3.5	6	7	76
More than 4,000 mg.hr. radium alone	90	3	3.3	8	8.8	79
Less than 4,000 mg.hr. with x-ray	113	5	4.4	6	5.3	102
More than 4,000 mg.hr. with x-ray	292	4	1.3	20	6.8	268
X-ray alone	41		--		--	--
Total	621	15	2.6	40	6.9	525 (90.5%)

In 126 cases, radium treatment was carried out in the face of low-grade fever (in excess of 37.4° C.) and/or a rapid sedimentation rate (30 minutes or less); 19, or 15 per cent, of these patients developed febrile reactions classifiable as severe or moderate. However, radium treatment was usually postponed in cases in which a temperature elevation existed.

With regard to the patients who received deep x-ray therapy either alone or in addition to radium, see Table II. Immediate reactions to radium have just been discussed. Immediate reactions to x-radiation were classified as *severe* when the patients were so prostrated or overwhelmed by the therapy that death ensued within a few days, or weeks, or a month or two at most; when nausea, vomiting, and diarrhea were so severe that considerable hospitalization was required; and when the patients were so sick that marked weight loss

blood supply. This in turn may lead to radionecrosis. Examples of this type of reaction are a persistent central necrosis of the cervix (without cancer) with its attendant inflammatory concomitants; ulceration of bowel or bladder walls,⁵ often with subsequent persistent hemorrhage from bladder or rectum (inelastic arterioles); rarefaction of bone, even fractures^{6, 8}; or occasional perforation of a viscus,⁷ sometimes with subsequent peritonitis, sometimes with fistula formation. There may, of course, be longtime specific effects upon tissues which prevent their repair other than diminution in blood supply, but in all probability the latter is the most important.

Other undesirable late effects have to do with the building up of connective tissue masses, or constricting scar tissue condensations; these reactions not infrequently cause partial or even complete bowel obstruction. Fibrosis of muscles sometimes interferes with certain motions. A striking though relatively harmless manifestation of this type of reaction is often to be found in the abdominal wall through which the roentgen rays have passed.¹⁰ It may become 2 to 3 times its former thickness and very dense, fibrous, and unyielding. The overlying skin is likely to be thin and telangiectatic.

No doubt, infection often contributes to the heavy condensations of connective tissue in the parametrial and uterosacral ligaments, so that it is really impossible to resolve completely the various tissue reactions according to their various etiologic components. It is also often very difficult, if not impossible, to distinguish between irradiation fibrosis and cancerous infiltration upon ordinary pelvic examination.

Radiation Technique

Since 1931, a relatively standardized technique has been employed at the University of California Hospital. Most patients have received deep x-ray therapy first. Both 200 kv. (constant potential) and 1,000 kv. machines have been used. The factors have been as follows: The 200 kv. radiations were from a General Electric X-P tube activated by a constant potential apparatus at 200 kv. and 15 Ma., and filtered through the wall of the tube (0.2 mm. Cu. equivalent) and 0.2 mm. Sn., 0.25 mm. Cu. and 2 mm. Al. or 0.5 mm Cu. plus 1 mm. Al. Supervoltage radiations were from the Sloan high frequency generator, operated at from 600 to 1,200 kv. and filtered through the tube wall of 1.5 mm. Cu. plus 3 mm. steel, and then through 2 mm. Pb., 1 mm. Cu., and 1.5 mm. Al. The skin target distance used is 80 cm.

During the 14 years, 1930 to 1945, under review, the roentgen dose has been gradually increased⁹ so that for the last 4 to 5 years about 3,000 r. (measured in air) has been delivered to each of four fields (10 by 15 cm.), two anterior and two posterior. In this study, no patient is considered to have received deep therapy who has received less than 1,000 r. to each of four pelvic fields. Generally three weeks have been allowed for recovery after the termination of x-ray therapy before the insertion of radium. The first radium treatment has usually consisted of an intrauterine tandem of three 50 mg. capsules of radium for 3,000 mg. hr. (Screening: platinum 0.5 mm., rubber 2.0 mm.) The second treatment has usually been given two weeks later and has consisted of a plaque containing 100 to 150 mg. placed against the cervix for 1,500 mg. hr. (Screening: platinum 0.5 mm., brass 1.0 mm.) This dose has been increased or decreased according to circumstances. There have also been selected groups of patients who have received roentgen therapy alone (Stage IV cases), or radium alone (growth of small volume, particularly in elderly women). The entire study includes 621 patients with cancer of the cervix.

Immediate Reactions

Since the only significant immediate reactions to *radium* were those of a febrile character, only these are considered. Immediate reactions to radium classified as *severe*: development of a pelvic abscess (such abscesses were com-

Late Reactions

Late reactions to irradiation were considered to be those which developed after the patient presumably had recovered from the immediate effects of therapy. It must be realized that a single reaction may be represented in two places in these statistics, e.g., a bowel obstruction also may be a connective tissue reaction when it is due to radiation. It will be noted that most late reactions can be explained, in great part, on the basis of the proliferative effect of radiation upon connective tissue, giving rise to obstructions or to markedly diminished blood supply. Some late reactions were due to the consequences of inflammation.

Bowel Obstructions

In this series there were 38 bowel obstructions which, in our judgment, were not due to cancer; ten of these obstructions were severe enough to necessitate colostomy. There certainly were many more partial obstructions, such as those of the rectum, which did not produce enough symptoms to be of note or to cause them to be listed here. Most of the obstructions were located in the neighborhood of the rectosigmoid junction opposite the cervix. This is not surprising when we consider that this section of bowel must receive the largest combined effect of radium and x-ray. Table IV confirms the impression that dose was a large factor here since it showed that the incidence of obstruction increased as the amount of irradiation was increased by the addition of larger and larger amounts of x-ray to radium therapy.

TABLE IV

TYPE OF THERAPY	PATIENTS	OBSTRUCTION	PER CENT
X-ray alone	41	0	0
Less than 4,000 mg.hr. radium alone	85	0	0
More than 4,000 mg.hr. radium alone	90	4	4
Less than 1,500 r. \times 4F plus radium	24	0	0
Less than 3,000 r. \times 4F more than 1,500 r. plus radium	166	9	5
More than 3,000 r. \times 4F plus radium	215	25	12
Total	621	38	6.1

The table also shows that obstruction did not occur in the small group of cases in which x-radiation alone was used, but the addition of x-ray in larger doses to radium therapy significantly increased the number of obstructions.

Connective Tissue Reactions

Condensations of tissue which were significant enough to cause signs or symptoms and which were apparently the result of irradiation changes in the vessels are considered under the heading of connective tissue reactions. In this group, we have also placed reactions in which there was a proliferation of connective tissue under radiation stimulus to such a degree that significant symptoms resulted. Included, then, are such difficulties as bowel or ureteral obstructions, lymphatic obstructions, etc. There were 46 such reactions (Table V).

The table shows that the "connective tissue" reactions were more common after larger doses of irradiation, especially when radium was used also.

occurred. Whenever the skin reactions were so marked that skin grafts proved necessary the reaction was also considered severe. Under *moderate* reactions have been included: severe skin reactions which did not require skin grafts and which were not associated with severe generalized reactions; reactions in which diarrhea, nausea, vomiting, anorexia, and prostration were sufficiently marked to make the patients quite ill, but not to a degree demanding hospitalization. Whenever the diarrhea, nausea, vomiting, anorexia, and weight loss caused little disturbance, or failed to appear at all, the reaction was classified as *mild*. Of the 409 patients who received deep x-ray therapy either alone or in combination with radium, 10 per cent had severe reactions, 30 per cent moderate reactions, and 60 per cent mild reactions. In Table II an attempt is made to correlate the degree of immediate reaction to x-radiation with the amount of radiation given. Curiously enough, no significant differences could be determined when the figures were handled in this way. (However, at times, therapy was stopped temporarily or abbreviated because of severe reaction. This would increase the number of severe reactions with lower doses of x-ray in this table.)

TABLE II. REACTIONS TO X-RAY THERAPY

DOSE	SEVERE		MODERATE		MILD		TOTAL
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
Less than 1,500 r. \times 4F	7	15	11	24	28	61	46
More than 1,000 r. \times 4F							
Less than 2,000 r. \times 4F	19	11	41	24	106	65	166
More than 1,500 r. \times 4F							
More than 3,000 r. \times 4F	14	7	70	35	113	58	197
Totals	40	10	122	30	247	60	Total 409

In Table III, the cases were rearranged in order that a comparison might be made between the immediate reactions in patients treated with the 1,000 kv. machine and those treated with 200 kv. x-rays. The incidence of severe and moderate reactions was only slightly higher for those treated with the 1,000 kv. machine.

TABLE III

MACHINE	PATIENTS	SEVERE		MODERATE		MILD	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
1,000 kv	243	36	15	33	30	174	55
200 kv	99	11	11	21	21	67	67

Part of the difference between the 1,000 kv. machine and the 200 kv. must be attributed to the fact that the 1,000 kv. machine has been used more recently when larger doses of x-ray have been given. It is the general feeling of many radiologists that the 1,000 kv. machine enables one to deliver a larger dose to the pelvis with less skin reaction, particularly in those with very thick abdominal walls.¹⁰

Eighty-eight patients were treated through six fields, which included two lateral ports in addition to the usual four pelvic ports. In this group, severe and moderate immediate reactions occurred in 15 per cent and 34 per cent, respectively, figures not significantly different from those for the four-field technique. In some instances the immediate reaction to irradiation was so severe that death ensued shortly after. These cases are discussed later in a section on mortality.

nation. The group also includes patients who had bladder bleeding of significant enough degree to warrant treatment. There were 48 patients in this group. They are reviewed in Table VII.

TABLE VII

TYPE OF THERAPY	PATIENTS	BLADDER REACTIONS	PER CENT
X-ray alone	41	1	2.4
Less than 4,000 mg.hr. radium alone	85	2	2.3
More than 4,000 mg.hr. radium alone	90	9	10.0
Less than 4,000 mg.hr. with x-ray	123	3	2.4
More than 4,000 mg.hr. with x-ray	282	33	11.7
Total	621	48	7.7

This table shows the relation of bladder reactions to larger doses of radium. Forty-two of the forty-eight bladder reactions occurred among the 374 patients who received more than 4,000 mg. hr. of radium.

Fractures

In this series there were five hip fractures and one fracture of the symphysis. There probably were other such fractures which were not recognized as such. In addition, there was a considerable number of patients who complained of pain in their hips and whose x-rays showed osteoporosis of the hip bones without evidence of fracture.

Fractures of the neck of the femur associated with roentgen therapy have been described by others.^{6, 8} There is agreement that they are due to endarteritis which in turn leads to osteoporosis and increased fragility. X-ray pictures at the time and subsequent events have usually proved these fractures not to be due to metastases.

Three of the five hip fractures occurred among eighty-eight patients who received six-field therapy (i.e., which included two lateral portals). The other two patients who developed hip fractures received 3,400 r. to four fields and 2,750 r. to four fields respectively. All five received radium therapy.

The patient with the fractured symphysis received 6,274 mg. hr. of radium plus 2,500 r. to one anterior and one posterior field.

The hip fractures, then, were associated with high doses of x-ray and were more common with six-field therapy. As one might expect, no fractures occurred among the patients who were treated with radium alone, since the action of radium placed in and about the cervix could hardly include tissues as far removed as the bony walls of the pelvis.

Muscle Reactions

A number of the patients in this series suffered from rather severe late "muscle reactions" as indicated by difficulty in moving extremities, inability to stand erect, etc. Such difficulties were thought to be due to fibrosis in the muscles and to decreased vascularity. It is certain that many of the patients in the series have had muscle reactions of a milder degree than is considered here. There were fifteen "muscle reactions" noted to be of considerable degree. Eleven of these were found among the patients who received more than 3,000 r. to four fields with radium and all fifteen received more than 1,500 r. with radium. Eight of the fifteen occurred among the eighty-eight patients who received six-field therapy.

Thus, the severe muscle reactions were associated exclusively with patients who had received x-ray therapy, especially those who had received the larger doses of six-field therapy.

TABLE V

TYPE OF THERAPY	PATIENTS	CONNECTIVE TISSUE REACTIONS	PER CENT
X-ray alone	30	0	0
Less than 3,000 r. \times 4F			
X-ray alone	11	1	9
More than 3,000 r. \times 4F			
Less than 4,000 mg.hr. of radium alone	85	0	0
More than 4,000 mg.hr. of radium alone	90	5	5.5
Less than 1,500 r. \times 4F plus radium	24	1	4.1
Less than 3,000 r. \times 4F	166	10	6
More than 1,500 r. plus radium			
More than 3,000 r. \times 4F plus radium	215	29	13.5
Total	621	46	7.4

Colitis, Proctitis, Rectal Bleeding

Commonly, late complaints were associated with the bowel, and here patients who had either marked colitis, proctitis, or rectal bleeding are grouped together. Again, it is to be remembered that there were many patients who suffered from mild degrees of these complaints who are not considered here (Table VI).

TABLE VI

TYPE OF THERAPY	PATIENTS	COLITIS, PROCTITIS RECTAL BLEEDING	PER CENT
X-ray alone	41	3	7.3
Less than 4,000 mg.hr. radium alone	85	1	1.1
More than 4,000 mg.hr. radium alone	90	2	2.2
Less than 1,500 r. \times 4F plus radium	24	1	4.1
Less than 3,000 r. \times 4F more than 1,500 r. plus radium	166	18	10.8
More than 3,000 r. \times 4F plus radium	215	51	23.7
Total	621	76	12.2

This table shows an increase in the numbers of intestinal reactions when x-ray in larger doses was added to radium treatment.

Bowel Ulcers

Isolated bowel ulcers, apparently due to local necrosis of mucosa from irradiation, occurred in ten cases. There were none of these among the 175 patients treated with radium alone and none among 99 patients treated with x-ray and less than 4,000 mg. hr. of radium. However, all ten occurred among 273 patients who were treated with more than 4,000 mg. hr. of radium combined with x-ray in excess of 1,500 r. to four fields. Most of these bowel ulcers, as might be expected, occurred high in the rectum or in the region of the recto-sigmoid junction, areas which received a large sum of irradiation from the two sources.

Urologic Complications

The urinary bladder was frequently involved in late reactions to irradiation. In this series are included those patients whose cystitis was apparently due to irradiation as revealed, in the greatest number of patients, by cystoscopic exami-

Mortality

Nineteen patients died as a consequence of irradiation (Table IX), and two others probably died of the effects of radiation. While all of these deaths were not due directly to the rays of radium and/or x-ray, there were several deaths attributable to such action since at autopsy or surgery nothing was found except the extreme destruction of cancer cells. In the remainder of the patients, the radiation apparently caused enough changes to precipitate death which took place in a few days to a few months following completion of treatment. No death was included in this group in which it appeared reasonable that cancer alone might have been the responsible factor. Probably there were other deaths, hastened by irradiation which have not been included.

In this series, 621 patients have been considered. Fifty of these patients received surgery as a major portion of their therapy, and therefore, they received irradiation primarily to clear infection and usually in small amounts. The 21 deaths considered here occurred among the other 571 patients, which gives a mortality rate of 3.7 per cent.

TABLE IX.—MORTALITY

CAUSE OF DEATH	RADIUM	X-RAY
1. Pyeloureteritis with uremia	5,200 mg.hr.	1,700 r. 4F
2. Hemorrhage (immediately after x-ray)	1,547	1,600 r. 4F
3. Perforation of sigmoid after acute peritonitis	3,027	1,520 r. 4F
4. Pelvic abscess	2,680	1,760 r. 4F
5. Pelvic abscess	2,233	0
6. Perforation with generalized peritonitis	4,558	3,160 r. 4F
7. Acute peritonitis	0	3,476 r. 2F
8. Severe immediate reaction with prostration	4,732	2,500 r. 4F
9. Severe immediate reaction with prostration	0	3,000 r. 2F
10. Severe immediate reaction with prostration	0	3,500 r. 2F
11. Severe immediate reaction with prostration (probable)	4,059	1,800 r. Lat. F 3,700 r. 4F
12. Abscess drain to peritoneum	6,344	3,000 r. 4F
13. Pelvic abscess with peritonitis	4,500	3,000 r. 4F
14. Perforation with cul-de-sac abscess	5,000	3,000 r. 4F
15. Cul-de-sac abscess	3,375	3,050 r. 4F
16. Severe immediate reaction with prostration	3,800	3,300 r. 4F
17. Severe colitis (probable)	5,000	3,550 r. 4F
18. Intestinal obstruction	4,500	4,050 r. 4F
19. Pyelonephritis, hydronephrosis, prostration	3,000	3,100 r. 6F
20. Perforation with peritonitis	4,500	3,550 r. 4F
21. Neocolic fistula, prostration	4,000	3,850 r. 4F

In summarizing the death causes then :

Pyelonephritis, uremia, etc.	2
Hemorrhage	1
Pelvic abscess, plus or minus peritonitis	5
Bowel perforation	4
Peritonitis	1
Prostration	6
Obstruction	1
Neocolic fistula	1

The chief causes of death were prostration during or immediately following roentgen irradiation (6 cases); the end results of infection, probably initiated at the time of radium application, or at least aggravated by this procedure (5 cases); and bowel perforation (4 cases). It should probably be possible to avoid "prostration" by more careful attention to the patient during her therapy with prompt interruption if her general condition appears to be deteriorating abnormally. Possibly smaller doses over longer periods of time could be used in the more sensitive individuals. It should also be possible to reduce the number of deaths due to infections by more careful preparation of the patient before

Fistulas

There were sixteen fistulas which seemed to be the result of irradiation changes, i.e., loss of vascularity with consequent necrosis. Of these, seven were rectovaginal, four were vesicovaginal, and five were in miscellaneous locations including an enterovaginal fistula. These figures represent an incidence of 2.5 per cent.

The association with type of therapy is summarized in Table VIII.

TABLE VIII

TYPE OF THERAPY	PATIENTS	FISTULAS	PER CENT
X-ray alone	41	0	0
Less than 4,000 mg.hr. radium alone	85	1	1.1
More than 4,000 mg.hr. radium alone	90	0	0
Less than 1,500 r. \times 4F plus radium	24	1	4.1
Less than 3,000 r. \times 4F more than 1,500 r. plus radium	166	6	3.6
More than 3,000 r. \times 4F plus radium	215	8	3.4
Total	621	16	2.5

The fistulas were found, then, among the patients who received a combination of x-ray therapy and radium. Apparently factors other than dose must have operated since an increased incidence of fistula was not clearly associated with larger doses. (Variations in technique not discernible in our analysis may have been responsible). The figure given here may be high since on some occasions it was difficult to be sure that the fistula was due to irradiation and not to cancer.

Radiation Necrosis

Almost complete noncancerous necrosis of the cervix followed by severe hemorrhage or abscess formation occurred in at least five patients, one of whom was treated with radium alone, the others having been given average doses of radium and x-ray in combination. Interestingly, at postmortem examination, such patients showed no viable cancer cells or else such examination revealed malignant cells which were apparently greatly damaged.

1,000 Kv. and 200 Kv. Machines

The 1,000 kv. machine and the 200 kv. machine were compared in the review with respect to each of the reactions noted. In most instances there were no significant differences. However, some difference in result was noted in the review of bladder reactions. Two hundred forty-three patients were treated with unmixd 1,000 kv. irradiation and 99 patients were treated with unmixd 200 kv. irradiation.

MACHINE	PATIENTS	BLADDER REACTIONS	PER CENT
1,000 kv.	243	28	11.5
200 kv.	99	3	3.0

The slightly higher incidence of bladder reactions in cases in which 1,000 kv. x-radiations were employed is difficult to explain and may well be due to chance—we are not inclined to attach any particular importance to it.

as the dose of radium and x-radiation increased (Table X). Possibly even larger doses would result in a still larger number of survivors, yet certainly a point would be reached where the increasing number of radiation complications would more than cancel the advantages.

A number of factors have been considered in connection with our search for means of reducing the incidence and severity of irradiation complications. There were 42 patients who had a significant anemia (hemoglobin less than 60 per cent) at the onset of therapy; 9 of these survived for more than 5 years. This is a lower survival rate than that of the whole series, but the number of cases is too small to be convincing. There were 92 patients who had fever (37.4° C. or more) and/or a rapid sedimentation time (18 mm. in 30 minutes or less) before irradiation. Only twelve of this group survived the five-year period. While such factors as fever and anemia appear to be related to a poor prognosis, they may well have been incidental only, since anemia and infection are more likely to be present in the more advanced cases. However, it would seem worth while to make every effort to combat anemia and infection before treatment is instituted whenever possible.

The increased incidence of late complications in and about the cervix (necrosis, obstructions of the rectosigmoid, etc.) in cases in which radium and x-ray were combined, particularly in the larger doses, suggests that these tissues were sometimes overirradiated. We believe that a reduction in dose is in order. Factors such as screening, intensity, duration of treatment, interval between treatments, etc., may well play a part in this connection.

Efforts should also be continued to determine the radiosensitivity of tumors since reduced amounts might frequently be in order. Indeed, this can sometimes be arranged on the basis of clinical response, although obviously it would be unwise to place too much reliance upon such an evaluation. Studies of serial biopsies or vaginal smears during the course of treatment might possibly prove more reliable.

Other measures which deserve further investigation or trial are the antibiotics (disappointing so far), the role of palliative surgery in cases of irradiation necrosis without recurrence, continuous hospitalization during roentgen radiation therapy, the determination of isodose curves for the method of treatment in use so that overirradiation can be avoided on a more precise mathematical plan.

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radium treatment, and constant attention to the avoidance of undue manipulation and injury of the cervix during biopsy, examination, and radium insertion. Penicillin and the sulfonamides have been used extensively without appreciable result.

Irradiation necrosis is probably responsible for bowel perforation. Complete prevention is unlikely to be achieved if we are to provide sufficient irradiation to be effective.

Discussion

It is apparent that radiation therapy for cervical cancer, when provided by the technique employed at the University of California Hospital, carries with it a distinct morbidity and mortality. Indeed, these complications have been sufficiently prevalent and distressing to stimulate us to seek ways and means of avoiding them. While we doubt that complications can be completely eliminated as long as radiation in effective doses is employed, we do feel that searching analysis of present methods and results can lead us to some improvements. In general, the severity of reactions increased as the dose increased, though this was not particularly convincing with regard to immediate reactions in our series of cases. This principle was borne out quite clearly with regard to late reactions.

Radium alone, as pointed out earlier, produced little significant general reaction, but its use, either directly or indirectly, sometimes caused the induction or exacerbation of infection, which occasionally was serious enough to cause death. Local destruction of tissue, fistula formation, etc., were not common in our cases from radium alone. Roentgen therapy often caused a general reaction, and sometimes produced so much prostration and general metabolic disturbance that death followed. It also produced proliferative changes in the normal connective tissue structures, not infrequently to such an extent that obstructions resulted, or necrosis ensued due to endarteritic changes with consequent reduction in the vascularity of the tissues. The incidence of complications was definitely greater in cases in which both radium and x-ray were used, and also increased as dose increased. Undoubtedly overirradiation, particularly of the cervix and immediately surrounding tissues, was often present. We believe that where x-radiation of effective proportions is added to an established radium technique—and in general this is the evolution of the treatment of this disease during the last fifteen years—thought should be directed toward reducing the irradiation to the tissues within the effective range of the radium, lest these tissues receive a lethal dose from the combined sources.

TABLE X

RADIUM MG.HR.	X-RAY \times 4F	PATIENTS WITHOUT SURGERY	ALIVE 5 YEARS	PER CENT
Less than 4,000	0	46	6	13
More than 4,000	0	70	20	29
Less than 4,000	Less than 3,000 r.	43	10	23
Less than 4,000	More than 3,000 r.	34	11	32
More than 4,000	Less than 3,000 r.	128	46	36
More than 4,000	More than 3,000 r.	115	47	41
Total		436	140	

Statistics for the 436 patients in this series who were treated radiologically only, more than five years ago, show that the percentage of survivals increased

able effects of treating the cervix are to be noted, and at least one group of writers ascribe to cervicitis an important role in the production of chronic parametritis.^{31, 66}

The "apparent precipitating cause" of the symptoms of pelvic congestion, as noted by the patient, is shown in Table I. The figures indicate "abortion" and "childbirth" as the second and third in relative importance. Miscarriage, especially induced abortion, has been frequently cited in the past as the cause of chronic parametritis^{6, 9, 63} and indeed this seems to be a common clinical assumption.

Parturition at full term may lead to congestion as a result of weakened pelvic supports, but this mechanism can hardly explain congestion or "parametritis" after abortion. The persistence of a true infection in the parametrium for years after a miscarriage likewise seems a hardly tenable hypothesis. It seems better in those cases dating their pelvic symptoms from an abortion to ascribe them, as Cotte has done, to a "postpuerperal phlebitis" and permanent injury to local vascular structures.

TABLE I. APPARENT PRECIPITATING CAUSE

	MARRIED	SINGLE	SEPARATED	TOTAL
Marriage	17			17
Marital discord	5		1	6
Separation from husband	4			4
Engagement		2	1	3
Divorce			3	3
Direct coital relationship	5	1	1	7
Childbirth	9			9
Abortion	10	1	1	12
Tragedy in family	1	4	1	6
Accident to patient	2		2	4
Operation on patient	2	1		3
No apparent cause	23	7	1	31
	78	16	11	105

4. *The Estrogens as a Cause of Hyperemia.*—

The part played by the estrogens, and perhaps progesterone, in the etiology of pelvic congestion requires careful thinking and precise statements. In particular, distinction must be made between the estrogens in normal quantities as essential prerequisites for the condition to develop and the estrogens in excessive amounts as the specific causative factors.

a. *The Role of Normal Quantities of Estrogens:* After the removal of the ovaries or the suppression of their function by radiation or by their exhaustion at the menopause, signs and symptoms of congestion of breast and pelvis diminish. Within a few months there remain only, and that rarely, some of the "neuralgic" complaints, atypical vaginal pain, coccydynia, and breast tenderness. The engorgement, backache, and leucorrhea soon disappear. This change is surely correlated with the loss of ovarian activity.

Furthermore, it is evident that the peak of congestive symptoms in the menstruating woman occurs in the days before the onset of each period. It is probable that this rhythmic increase in symptoms in the premenstruum is due to the physiologic increase in blood estrogen or perhaps progesterone concentration. This, however, is not evidence of unphysiologic levels of hormone as the cause.

b. *The Possibilities of Hyperestrinism:* In many of these patients the clinical picture closely resembles what has been called "premenstrual tension." For the latter condition an estrogen excess has been assumed,^{26, 38} perhaps as a result of overproduction or as the indirect result of a vitamin B deficiency.³

2. *Mechanical Factors.*—

Various mechanical factors may evidently affect the flow of blood through the pelvic vessels and thus alter local intravascular pressure, especially in the veins. Changes in any of the mechanical factors result in rapid, although temporary, variations in the symptoms of pelvic congestion.

a. The Standing Position: A most convincing demonstration of the effect of gravity is the relief experienced by the patient with pelvic congestion when she lies down. Conversely, leucorrhea, menstrual bleeding, and backache are notoriously increased by long periods of standing. It seems almost obvious that alterations in position affect symptoms through a change in venous pressure and resulting change in degrees of congestion.

b. Fatigue: The factor of fatigue was evident in many of the cases of this series and is frequently given as a symptom by these patients. It has been accorded importance by many other observers.^{6, 9, 20, 21, 22, 28, 30} Fatigue, resulting in a loss of muscle tone, may simply make the effects of the standing position more apparent. On the other hand, it may result in increased nervous tension and so add to the effects of the "vasomotor impressionability."

c. Malposition of the uterus has been held a factor in congestion by French, German, and American writers.^{6, 9, 14, 20, 21, 22, 29, 55, 73} The malposition may cause congestion through a kinking of the veins, by adding to the effects of gravity as in descensus, or simply through the often associated defective fascial support of the pelvic vessels.

It is difficult to evaluate the importance of malposition in the present series. A retroversion of appreciable degree was present in a third of the cases. In at least ten cases a suspension had been performed prior to the first visit of the patient and in fifteen cases this operation was subsequently performed. The results in these ten previously performed suspensions were obviously unsatisfactory and in those performed subsequently not completely so. Dickinson¹⁷ on the basis of one hundred cases denies that the incidence of retroversion is any higher in a series of cases of "chronic parametritis" than among office gynecologic patients in general.

The observation of a few striking cases, however, makes it appear probable that retroversion is at times the principal, although not the sole, factor. The diminution in backache after the insertion of a pessary is a common observation and in two cases of this series a menorrhagia disappeared with the same type of therapy. Cotte⁹ graphically demonstrated by Lipiodol injection the reduction in size of the uterine cavity which followed suspension of the enlarged congested uterus. This change in size seemed clinically evident in similarly treated cases of this series. Retroversion is not, therefore, to be regarded as the source of symptoms, but in at least some instances predisposes to the congestion which produces the symptoms.

d. Constipation: The anastomoses between rectal and uterine venous systems have been referred to and the point made that disorders of circulation affecting one area would be evident in the other also. Rectal symptoms and the frequent presence of hemorrhoids have been reported in cases of uterine congestion. Conversely, constipation with straining at defecation has been suggested as a source of pelvic congestion^{4, 5, 9, 54, 62} and seems an important factor in some cases.

3. *Inflammation.*—

Inflammation may affect local circulation in two ways, through the hyperemia of the active stage of the infection and through permanent damage of vessels and lymphatics. The former is certainly the more obvious factor in the pelvis, but the latter possibly more important.

The difficulty of separating the effects of congestion and of inflammation in cases of severe cervicitis with pelvic pain has already been discussed. The favor-

TABLE II. TYPES OF BIRTH CONTROL IN MARRIED GROUP

No birth control	31
Condom	10
Douche	10
Interruptus	6
Diaphragm	3
Abstinence	7
No information	11

Masturbation was not included in the routine history of these cases on account of the obvious difficulty of eliciting such data in an ordinary clinical gynecologic history. Since labial hypertrophy, especially when unilateral, has been interpreted as indicative of excess in this practice,^{15, 41} it is interesting to note how frequently this hypertrophy, especially in its more marked degrees, was recorded in the single women of the series (Table III). Fränkel,²³ in particular, believed masturbation to be a factor in producing "chronic parametritis" in the unmarried.

TABLE III. INCIDENCE OF HYPERTROPHY OF LABIA MINORA

	TOTAL CASES IN GROUP	SLIGHT OR QUESTIONABLE HYPERTROPHY	MARKED HYPERTROPHY
Married	78	11	3
Single	16	8	4
Separated	11	1	2

Dyspareunia, in the form of frigidity or painful intercourse, has already been noted as of nearly universal occurrence in these patients (Section II, Table XX). These symptoms are doubtless the result of the congestion but also in that they interfere with normal coital physiology are perhaps the most important cause of the continuation of the congested state.

In summary, it appears that any form of sexual stimulus, whether this be direct or simply psychologic, which produces a pelvic hyperemia and does not shortly provide for relief from it, will lead to a state of congestion, which with constant repetition will become chronic.

b. Nonsexual Nervous System Factors: Certain nonspecific psychological factors have also been suggested as causes of pelvic congestion. These have included fear of pregnancy or infection, hate or dislike of partner, marital incompatibility, conflicts and anxieties of all sorts.^{16, 40, 42, 49, 51, 76}

TABLE IV. INCIDENCE OF SPECIAL SOCIAL PROBLEMS

	MARRIED	SINGLE	SEPARATED	TOTAL
Marital discord	22			22
Recent divorce			8	8
Separation from husband	6			6
Special sexual problems	3		1	4
Engagement problems		3		3
Premarital affairs	1	1		2
Death or illness in family	3	3	1	7
Accidents to patient	2		2	4
Conflicts in job	1	1		2
Total cases with at least one obvious social problem	36	8	6	50

In about half of the patients of this series (Table IV) there was an obvious social problem, capable of producing a state of stress. In a few cases the actual

There is, however, no real evidence that the women with pelvic congestion have excessive activity of either follicles or corpus luteum. The menstrual periods are usually normal and when disturbed are as often scant as excessive. The pattern of endometrial tissue examined in this group of cases, as in that previously reported for cases of chronic mastitis (Taylor⁷¹), corresponds with that expected for the time of the cycle and hyperplasia is not characteristically found.

Hormone assays were not done in any of the cases of this study, but were carried out in several cases previously reported in which breast engorgement was the point of special interest but in which signs of typical pelvic congestion were incidentally present.⁷² In two such cases reported in 1942 (Taylor⁷²), and in seven cases in 1936 (Taylor⁷¹), complete assay was made of the full cycle of estrogen excretion, the tests being made on consecutive 72-hour samples. On the basis of these nine cases, representing breast engorgement, the painful "cystic ovary," and "chronic parametritis," no typical disorder of estrogen excretion could be discovered.

In spite of the temptation to ascribe excessive pelvic hyperemia to the estrogens there is no real evidence for such a view. It is far more likely that estrogen activity within a normal range provides the normal cyclical variations in vascular behavior upon which are superimposed the effects of abnormal mechanical conditions and abnormal sympathetic nervous system stimuli.

5. *The Sympathetic Nervous System.*—

The nervous system factors causing vasodilatation in the pelvis may apparently be specifically sexual or nonspecific emotional stimuli. Both of these groups have been considered extensively in the literature and were evident factors in this series of cases.

a. Sexual Factors in Pelvic Congestion: A variety of different circumstances within the area of sexual behavior have been held responsible, including excessive coitus^{6, 9, 10, 20, 21, 22, 28}; abstinence⁹; masturbation^{4, 9, 18, 23, 25, 27, 28, 39, 40, 49}; and contraceptive measures, particularly coitus interruptus.^{22, 24, 32, 33, 39, 40, 49, 61} Evidence from the present series of cases can be found to show that each of these causes is at least occasionally operative.

Psychological rather than local reflex stimuli in the production of hyperemia on a sexual basis have been assigned a prominent role by other writers.^{7, 39, 40, 49, 51} These are obvious factors, although it is perhaps going too far to agree with Lawson Tait who in 1883 warned against the possible ill effects of piano lessons on the ovary of the adolescent female.

Excess: In seven instances in the present series (Table I), an attack of acute pelvic discomfort appeared to be directly attributable to excessive sexual activity. In several of these the difficulty seemed to arise from unequal sexual requirements and capacities of husband and wife.

Abstinence: In four instances (Table I), chronic pelvic discomfort developed in young married women whose husbands were separated from them while in the army. These were all relatively mild cases with moderate pelvic discomfort and rapid improvement.

Contraception, as such, could not be held as responsible in any single case nor did the data on types of birth control employed point to any technique as especially harmful (Table II). The fact remains, however, that all birth control devices are at times capable of disturbing normal coital function and in this way must in some women be productive of disturbed vascular conditions in the pelvis. It is also conceivable that years of sexual activity without pregnancy may have deleterious effects.

These are remote possibilities, but in the absence of any other acceptable explanation of these tumors may not be entirely discarded. The history of the following patient, in whom the pelvic organs were inspected at three operations over a twelve-year period, is offered simply as an example of the possible evolution of this disorder.

Case Report

Mrs. R. K. was admitted to the Sloane Hospital in the Columbia-Presbyterian Medical Center on April 23, 1948. The patient, then 37 years of age, had been married since the age of 18 years. Her first child was born a year after marriage, and was delivered with great difficulty after a labor of four days. There followed three induced abortions at the ages of 21, 22, and 23 years. At the age of 24, she was delivered of a premature stillbirth weighing 2 pounds and 12 ounces, the fetal death resulting from a prolapsed cord.

From about the age of 23, she began to suffer from numerous gynecologic symptoms. These consisted in pain in the back and abdomen for a week before the periods, bilateral ten-day premenstrual swelling and tenderness of the breasts, pain in the right lower quadrant and increasing dyspareunia. For these she was operated upon at the Roosevelt Hospital at the age of 25 on May 21, 1936.

At this, the first operation, the following findings were noted: The fundus was of normal size, in second degree retroversion, with slight descensus. The cervix showed deep, bilateral lacerations without much infection. The uterosacral ligaments were noted as fibrous and sharply defined. Both tubes were patent but surrounded by a few adhesions. The right ovary showed a slight thickening of the capsule and a few small cysts, but was not enlarged. The operation consisted of a dilatation and curettage, a cauterization of the cervix, a right salpingo-oophorectomy, a round ligament suspension and a liberation of omental adhesions. The pathologic report showed normal endometrium and follicular cysts of the ovary.

During the next six years, the patient improved somewhat, but continued to complain of pains in the abdomen and back, dyspareunia, headaches, constipation, and severe nervous tension. During these years she also had two more miscarriages, the second of these at six months. On November 20, 1942, she reported herself two and one-half months pregnant. The pregnancy was uneventful but on account of a borderline contraction of the pelvic inlet and the history of an extremely difficult forceps delivery and of a stillbirth she was delivered on June 5, 1943, by cesarean section at Bellevue Hospital. At the time of the cesarean section no special abnormalities of the uterus were noted.

During the next three and one-half years the patient was seen only at rather long intervals. On Dec. 27, 1943, the uterus was noted as somewhat enlarged with the left adnexa still quite tender. During 1946 and 1947, the periods began to become heavier and to be associated with clots. A year later, at the age of 37, the patient returned to report that her menstruation had become very heavy, was lasting seven days and causing her to be confined to bed for two days each month. The dyspareunia was still very marked. Examination showed the fundus to be definitely enlarged; the cervix hypertrophied and the parametrium very tender. The patient was sent to the hospital for a hysterectomy.

At this, the third operation, performed at the Sloane Hospital on April 24, 1948, the left ovary was found slightly enlarged with a very corrugated appearance and several follicle cysts. The uterus was greatly hypertrophied and there appeared to be a small fibroid on the posterior wall. The operation consisted of a complete abdominal hysterectomy, left salpingo-oophorectomy, and the division of omental adhesions.

The pathological examination (Fig. 1) confirmed the increase in uterine size, the weight being 225 Gm. and the dimensions 12.5 by 8 by 6 cm. The corpus was symmetrically enlarged and exhibited near the fundus a diffuse area, whose texture on gross examination differed only slightly from that of the surrounding myometrium. A second more nodular area was noted in the right lateral uterine wall. The myometrium itself varied from 1.5 to 3.5 cm. in thickness and presented a grossly trabeculated, vascular, edematous cut surface. The left ovary measured 5 by 2.5 by 1.5 cm. The surface was studded with small cysts containing serous fluid. The cut section displayed also many small follicle cysts and one larger hemorrhagic

precipitating factor appeared to be a single incident or event, affecting perhaps the patient's sense of security, such as an accident or operation, the patient's own divorce, or the death of a relative (Table I). In a larger group there existed major social problems, particularly concerned with the marriage relationship and therefore difficult to separate from associated sexual problems, but undoubtedly the cause of a general state of nervous stress.

It seems certain that such factors as these, which now admittedly affect gastrointestinal blood supply, motility, and secretion should have a comparable effect on the smooth muscle and secretory cells of the pelvis. It is not, however, often clear whether the emotional manifestations in these patients are entirely the cause or may be in part the result of the vasomotor disorder in the pelvis.

Summary of Etiologic Factors

Pelvic congestion is, therefore, a disorder of the pelvic circulation with multiple causes, several of which may have to be present in a single patient to produce symptom-giving conditions. Predisposing constitutional factors are probably present in the autonomic nervous system and perhaps in the blood vessel structure of the susceptible patient. The tendency to congestion is increased by loss of support of the pelvic structures after parturition, by malposition of the uterus, possibly by damage to the veins from postpartum phlebitis, and by occupations requiring the erect position and leading to excessive fatigue. The estrogens maintain the pelvic tissues in a state receptive to those stimuli and their physiologic premenstrual rise places most of the complaints in that part of the cycle, but this disease is not due to any primary ovarian or other endocrine disorder. The autonomic nervous system is responsible for both acute and chronic vasodilatation as a result of unphysiologic sexual behaviors as well as nonspecific emotional states.

Chronic Congestion as an Etiologic Factor in the Origin of Neoplasms

The existence of a stage of fibrosis developing on the basis of a long-standing congestion in fundus, cervix, breast, parametrium, and ovary has been discussed. There remains to be noted the possibility raised by several writers of more definite neoplastic processes arising on this basis.

In a previous paper on chronic mastitis (Taylor⁷²), it was suggested that premenstrual engorgement could lead to a fibrosis or an adenofibrosis within which might arise foci of adenomatous proliferation of small ducts and acini. The morphologic similarity of adenofibrosis of the breast and adenomyosis of the uterus (Taylor⁷²) is striking, and for adenomyosis Moench⁵² has also postulated chronic congestion as the responsible cause. Finally, endometriosis, a neoplastic condition closely related structurally to adenomyosis has been theoretically ascribed by Meigs⁵⁰ to delayed pregnancy. The mechanism by which the latter is effective is conceivably the congestion of repeated menstrual periods unrelieved by pregnancy.

The morphologic similarity of these three processes, with their mixed proliferations of epithelium and of fibrous or muscular stroma, is quite apparent. Aschoff¹ drew attention to the analogies between these diffuse neoplastic conditions of breast and uterus and, as others have done, added "adenomyosis" of the prostate to the group.

Myomas of the uterus tend to occur in somewhat the same type of patient as does endometriosis, namely, in the unmarried or in the infertile. Many of the older writers held the absence of pregnancy as a contributory cause. Kehrer,³⁹ in particular, after a study of 500 cases, ascribed the growth of fibroids to the developmental stimulus of chronic hyperemia upon seeds of displaced embryonal cells.

Young's^{74, 75} approach and is of course essential in those cases in which a true parametritis of cervical origin is present.^{34, 36, 68} Glycerine tampons to reduce local edema are recommended by others.^{9, 20, 21, 61}

From the German concept of the disease as a fibrosis or spasm of the uterosacral ligaments there developed a number of methods of therapy, including massage^{9, 35, 67}; stretching of the uterosacral ligaments^{37, 61}; injection of the uterosacrals with Novocain and other substances^{32, 55, 69, 74}; and "episacral" nerve block.⁶⁰

c. Endocrine therapy in a very vague sense is mentioned by one or two authors.^{9, 20, 21} The androgens have been reported as very successful in what may be a special aspect of this syndrome, namely "premenstrual tension,"⁷²⁶ a treatment believed to be effective by neutralizing endogenous estrogens and so preventing fluid retention. Israel³⁸ advocated progesterone in "premenstrual tension." Cotte⁹ and Faure²⁰ mention radiation, a form of endocrine therapy when directed at the ovary in patients near the menopause.

d. Surgical procedures: For the more severe and resistant cases, numerous surgical procedures have been tried. The division of the uterosacral ligaments was advocated by a considerable list of gynecologic surgeons.^{5, 8, 53} Fränkel²⁵ added to this procedure the step of inserting omental fat between the cut ends of the ligaments to prevent the reformation of retractile scar tissue. Resection of the presacral nerve is approved by several French authors,^{6, 9, 12} but the results are considered unsatisfactory by Young.⁷⁵ Direct approach to the vascular system by ligation or excision of the dilated veins of the broad ligament has also been practiced.^{13, 19, 27, 56, 65} Suspension of the displaced uterus may be successful in some cases,^{4, 5, 35, 40} and Cotte⁹ has noticed the diminution in uterine size that follows this procedure. Hysterectomy is at times believed to be necessary, especially in the cases of uterine hypertrophy with advanced structural change.^{6, 20, 21, 22, 75}

Operations on the ovaries belong in a somewhat separate category. Partial or complete removal has been undertaken because of their increased size or their persistent tenderness or because of an assumed etiologic relationship between abnormally functioning ovaries and the pelvic congestion.^{6, 9, 20, 21, 22}

2. Results of Treatment in the Present Series.—

Since this series of cases has been slowly collected over a number of years and the evolution of the concept of the disorder has been a gradual one, the plan of treatment has been somewhat inconsistent. Furthermore, since only severe cases of the disorder have been included, the group includes a relatively large number of surgically treated patients. Nevertheless, the series contains for the most part patients observed over a long period of time, so that a fair idea of the course of the disorder and the effects of therapy is obtainable.

TABLE V. RESULTS OF TREATMENT IN CASES OBSERVED AT LEAST SIX MONTHS

	NUMBER OF CASES OBSERVED			NO	
		CURED	IMPROVED	CHANGE	WORSE
General treatment	30	0	14	15	1
General and local	10	0	6	3	1
Conservative abdominal surgery	14	0	5	9	0
X-ray of ovaries	2	0	2	0	0
Hysterectomy	2	1	1	0	0
Total	58	1	28	27	2

An analysis of the results of treatment is shown in Table V. It will be noted that in 58, or a little over one-half, observation was carried on for a period of

cyst. Microscopic examination of the tumor in the fundus and in the lateral walls showed bundles of fibromuscular tissue with some islands of endometrial glands and stroma.

The final diagnosis was diffuse hypertrophy of the myometrium, focal adenomyosis uteri, normal proliferative endometrium, follicle cysts of the left ovary, and hemorrhagic corpus luteum.

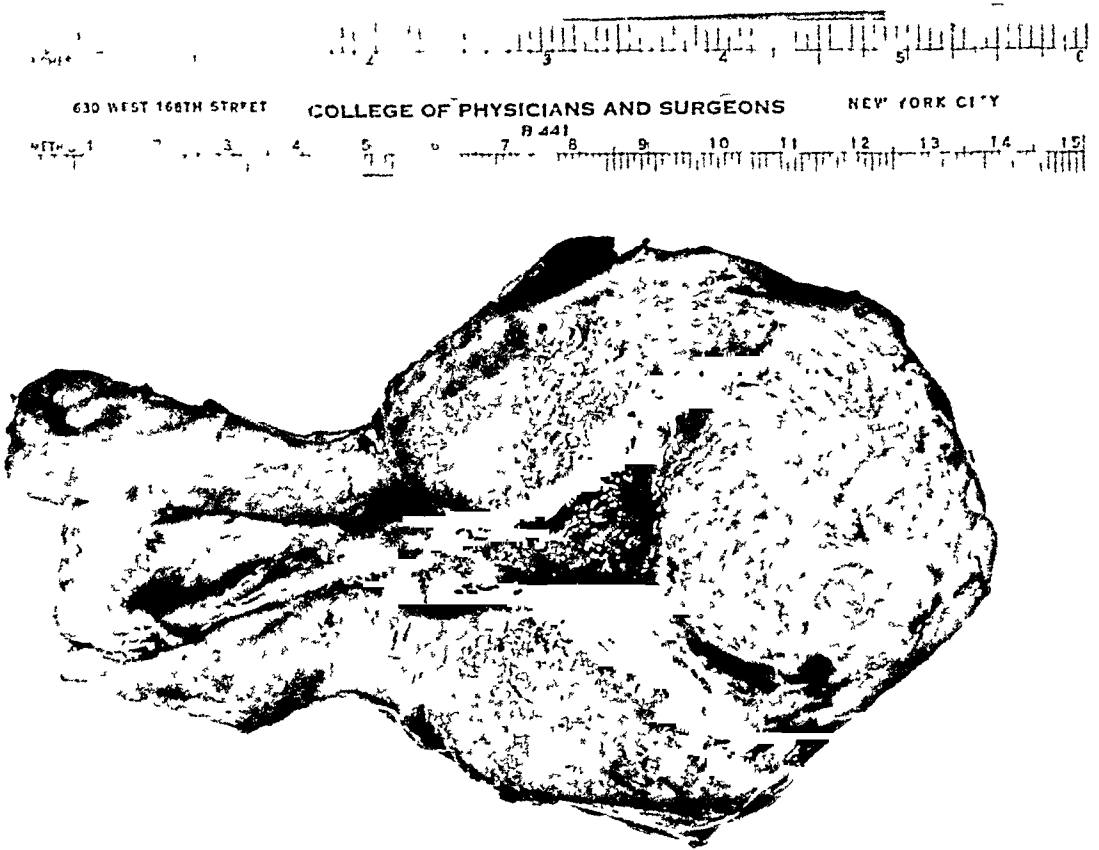


Fig. 1.—Uterus removed for adenomyosis after twelve years of observation for chronic pelvic congestion.

The Treatment of Chronic Pelvic Congestion

The various aspects of chronic pelvic congestion have been and remain notoriously resistant to treatment. The development of a rational plan of therapy depends upon the understanding of the underlying physiologic disorder and the multiple factors which contribute to it.

1. Previously Reported Methods of Therapy.—

The methods of therapy that have been reported have depended upon each writer's own conception of the nature of the disorder and upon the severity of a particular case. Certain previous methods may be noted as follows:

a. General Measures: The modern French writers are the ones most concerned with the patient's general health. They and some others emphasize the importance of physical rest^{9, 20, 21, 28}; of mental calm^{6, 22}; of mild exercise^{9, 17, 20, 21}; of attention to the diet^{9, 20, 21, 22} and the elimination of alcohol.^{6, 9} The regulation of intercourse is recommended by the French authors and genital rest principally by the Germans.^{23, 28, 30, 40, 41, 61}

b. Local measures are directed toward the clearing up of cervical infection, at tissue dehydration, and at the stretching or anesthetizing of the painful uterosacral ligaments. Treatment of the infected cervix is the central point in

(3) *The nonspecific factors of tension* are often inextricably mixed with those of the preceding category, but at times the cases seem clearly separable. The patients in this last group are often single or separated women, or married women near to their menopause. They almost invariably present special problems of family or occupational stress. The clinical aspect of this group approaches the picture described for "premenstrual tension" with prominent breast complaints, gastrointestinal or cardiac symptoms, and pronounced emotional manifestations.

b. An Evaluation of the Severity of the Condition: In many instances, episodes of pelvic discomfort may be transitory, affecting perhaps only one menstrual period, precipitated by circumstances that are quite temporary. To this category belong brief attacks of pelvic pain, isolated menstrual periods inexplicably associated with dysmenorrhea or excessive flow, and short episodes of breast or ovarian tenderness. These cases require no treatment except observation and reassurance.

At the other extreme are the patients who have suffered for many years from any or all of the characteristic symptoms of the disorder. In these, organic change appears often to be present which through injury to nerves, blood vessels, or myometrium renders cure impossible without surgery or the therapeutic suppression of the ovarian function.

c. Trial of the Simplest Therapeutic Measures First: A final point in policy is the avoidance of haste in the adoption of any radical procedure and the trial of the simplest measures first. With these general principles in mind, the following special therapeutic measures may be considered.

(1) *Local measures:* Treatment of chronic cervicitis is always indicated to reduce the leucorrhea and in some cases to diminish pain from the associated chronic lymphangitis of the broad ligaments. Other local measures such as glycerine tampons, hot douches, and diathermy have a dubious position in the therapy of this condition. Constipation should be eliminated so far as possible. Standing for long periods of time and exertion causing fatigue are definitely bad, but brief periods of exercise designed to improve pelvic muscle tone and circulation are perhaps helpful.

(2) *Regulation of sexual function:* In the presence of severe congestion the complete temporary discontinuation of intercourse seems essential, an interdiction which includes all forms of sexual excitation, both mental and physical, which might precede or be substituted for intercourse. An attempt should then be made to eliminate factors associated with disturbed coital function, such as unacceptable contraceptive measures, undue frequency, dyspareunia, and psychologic frigidity. The possible dangers of postponed pregnancy should be explained to young married women. When marital intercourse is resumed, it should be clear to the patient that she is probably predisposed to pelvic vascular disorder and coitus should be undertaken only when her mental and physical condition, particularly with regard to absence of fatigue, is favorable.

(3) *General health measures:* Attention to the patient's general manner of living, especially the strains imposed on her emotional and physical capacities, is essential. Many of these patients must be taught that they are constitutionally not equipped to live as intensely as they apparently desire.

Physical fatigue may in itself be an important factor in starting the whole chain of psychologic and physiologic disturbances. Vacations, involving freedom from work and responsibilities, may therefore be of greatest benefit.

The presence of emotional instability and of many extragenital "psychosomatic" symptoms necessitates a consideration of the patient's interpersonal relationships at home or at work. These aspects occasionally require the services of a specialist in psychiatry but more commonly seem to be problems of a type

at least six months, the average period being somewhat over three years. In exactly one-half there was no improvement. Of the other half there were varying degrees of amelioration but only one apparent "cure." Chronic pelvic congestion is evidently a persistent disorder, dependent upon the basic constitution of the patient, upon more or less unmodifiable psychologic factors, or upon conditions of living which the patient is unable to alter.

A slightly more optimistic outlook is possible if one accepts the impression of the writer, that the results in patients who made only one or two visits and were, therefore, not analyzed under "results" in Table V responded quickly to simple suggestions.

The different types of treatment as carried out (Table V) show approximately the same proportion of "improved" and "unimproved" cases as does the total series. Treatment involving major alterations in the anatomy or physiology of the reproductive organs, i.e., by hysterectomy or x-ray castration, give a better outlook and this impression is borne out by the experience with other more recent cases not included in this series. Patients having considerable cervicitis, comprising most of the cases in the category labeled "General and Local" in Table V, also showed a relatively better chance of improvement. The cases without local lesions, i.e., those treated only by "general measures," showed a high percentage of failures. Finally, the patients listed under "other abdominal surgery," including in particular those treated by partial removal of the ovaries, were usually unimproved.

3. *A Plan of Therapy.*—

Just as there is no single etiologic factor, there is no single method of treatment for the clinical syndrome based on congestion of the female reproductive tract. A plan of therapy for the individual patient must be built up from a careful evaluation of two aspects, namely, (a) the principal causative agent and (b) the severity or the duration of the condition.

a. The Determination of the Principal Causative Factor: The initial history and physical examination should be directed toward a preliminary broad classification of the case into one of three general categories, based upon the probable origin of the trouble. The three major causes are an organic lesion, unphysiologic sexual behavior, and nonspecific emotional tension. This is perhaps an oversimplification, but many cases fall readily into one of these simple categories. The classification is made by careful attention to the circumstances of origin of the symptoms, the presence or absence of extragenital complaints, and the physical findings.

(1) When *organic factors* are important, the onset of the condition is apt to be definitely referable to delivery or abortion. The symptoms will be largely limited to the pelvis without breast or other distant psychosomatic manifestations. Examination will disclose cervicitis, malposition and possibly hypertrophy of the uterus, and relaxation of the pelvic floor.

(2) *Disturbances in coital function* as an important factor should be suspected in cases dating the origin of their symptoms from the time of marriage, less commonly to the beginning of other sexual relationships. The symptoms in this group are chiefly pelvic, although there may be breast manifestations and some general psychosomatic and emotional reactions. A sexual factor is most apt to be the source of the difficulty when on examination there is found a marked tenderness of ligaments or ovaries, moderate "endocervicitis," but no other organic pelvic defects. The obtaining of the history on a few points of sexual behavior is properly postponed until after the examination at which time it is usually not difficult. This aspect of the problem cannot, if the patient is to be intelligently treated, be omitted.

uterus, cervix, ovaries, parametrium, and breasts. Evidence has been offered that this disorder may be present in only one of these areas and give characteristic local symptoms or may be more or less generalized giving a syndrome derived from the whole reproductive tract.

Evidence has also been given to show that the persistence of this functional vascular condition over many years may result in permanent structural change, consisting principally in proliferation of the connective tissue elements, producing either a fibrosis, as for example in the ovary and parametrium, or an hypertrophy, as for example in the corpus uteri and cervix.

The etiology of this chronic congestion depends on the multiple factors which may produce hyperemia, vascular dilatation, and stasis. Some of these are local and due to anatomic defects, gravity, and inflammation. Others involve several pelvic structures and apparently result from unphysiologic sexual behavior. Still others are quite general and seem to depend on emotional or other psychologic causes.

The treatment of this condition must be based principally on the elimination of the causative factors. These in many instances are determinable from the history or physical examination. As an adjuvant to this approach, various measures involving general or local dehydration may be tried. Finally, in a few cases in which structural change has apparently begun, surgery or ovarian radiation may be needed.

These disorders of the circulation and of the autonomic nervous system in the reproductive organs appear to be the basis of a considerable portion of all minor gynecology and include many conditions now commonly classed as endocrine or inflammatory. Within this field are mastodynia, premenstrual breast engorgement and certain types of "chronic mastitis," uterine congestion and hypertrophy, and many cases of menorrhagia, cervical hypertrophy, and the majority of cases of "endocervicitis," the congested and "cystic ovary," and many of the causes of dyspareunia, dysmenorrhea, and obscure pelvic pain.

The revaluation of gynecologic conditions to include this concept would constitute a major and, the writer believes, an essential revolution in gynecologic thinking.

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to be handled by any intelligent, sympathetic physician willing to devote his time to their solution.

(4) *Endocrine therapy*: The approach to the problem by way of the endocrines appears to be an indirect one, aimed not at the actual etiologic factor but against the physiologic mechanism by which the patient is maintained in a state susceptible to the precipitating cause.

The androgens have been reported to give good results, especially in premenstrual tension, apparently because of an inhibiting or neutralizing effect on ovarian function. Dehydration by the elimination of salt from the diet and the administration of ammonium chloride may be beneficial by preventing the excessive retention of fluid, resulting from normal premenstrual estrogen levels acting in the presence of abnormal vascular conditions induced by other factors.

In a small but definite group of patients the symptoms of the congestion syndrome are most pronounced just before the time of the menopause. Breast and pelvic discomforts may be eliminated by retiring the reproductive tract from the wear and tear of active participation in the psychologic problems of life by inducing an early menopause by x-ray. If such patients are carefully selected, the controllable symptoms of the menopause are far more tolerable than those of the congestion syndrome.

(5) *Surgery*: Surgical treatment should be reserved for cases of long standing and particularly for those in which organic change makes functional improvement improbable. Operative treatment will, therefore, be indicated in only a small fraction of these patients.

Repair of the pelvic floor is a proper procedure when relaxation and a third-degree retroversion with some enlargement of the uterus are present. The value of ligation or excision of broad ligament varicosities in this group is not clear. Presacral nerve resection has an undetermined place in the surgical treatment of these disorders. It may properly be combined with other types of indicated abdominal surgery but much further study of the pelvic sympathetic seems necessary before the value of this operation is established in this condition.

Operations on cystic ovaries should be avoided if possible since the symptomatic results are poor. In cases of persistent pain of long standing, other measures having failed, the surgeon may, however, be forced to some operation. If the pain is unilateral, the removal of one ovary may help. If bilateral, a resection of more than half of each ovary may be tried, but in the cases so treated further surgery seems often to follow.

Hysterectomy is indicated in a few cases of long standing, especially where there is menorrhagia or severe dysmenorrhea with an hypertrophied uterus. This operation is much to be preferred to any more conservative abdominal procedure when the need for preserving the reproductive function is past. The cervix should always be removed when hysterectomy is undertaken.

(6) *Prevention*: The idea of prophylaxis against congestion has been tentatively and theoretically put forward by a few writers. The concept of prevention is a good one, because undoubtedly this condition tends to persist when once established. Prophylaxis must be based on the early recognition and elimination of the etiologic factors just discussed. In more general terms it requires broad consideration of the strains imposed by present-day living upon women of the childbearing age and the perhaps unwise liberties that modern society is taking with the reproductive process.

General Conclusions

On the basis of a series of 105 cases, a description of the signs and symptoms of chronic hyperemia and vascular congestion has been given, as this condition affects the various parts of the female reproductive tract, the

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thus result. Technical errors, as improper apposition of tissues, excessively tight suturing, injudicious spacing of sutures, faulty knots, etc., all contribute toward defective scar formation. Cooke, in discussing wound healing, pointed out that tissue necrosis resulting from excessively tight suturing was probably a greater factor in the production of weak scar than were the infection or failure to close in layers.

Presumed causes of weak scar, such as the location of the uterine incision and the character of suture material are disputed. English workers seem to prefer classical section. Wyse of Germany, in 1905, stated that a bad cervical scar was worse than a fundal scar because of the marked thinning of the lower uterine segment. American obstetricians generally favor the low segment approach. Furthermore, Waters and Phaneuf believe that a transverse, low cervical incision is safer than a vertical one. Despite these various preferences, the critical observations of Falls, Schuman, and others revealed very little difference in results of the two types of cesarean section when comparable cases were analyzed.

Regarding suture material, opinions are also divided. Price, Kennedy, Babcock, and Potter advocate the use of nonabsorbable, nonirritating suture materials but the excellent results experienced by the user of "catgut technique" indicate that wound healing depends less on the material than on the method. Supporting this latter view is the work of Bowers, Burns, and Mengle with fine 5-0 chromic catgut suture in surgery of the gastroenteric tract, the biliary tract, in suturing of dura, tendon, nerve, and fascia and in surgery of children.

Other factors advanced as predisposing or contributing to weak scar are the influence of placental implantation over the scar and the effect of overdistention on the scar. In a well-healed scar, neither factors affect the scar in any way. In a defective scar, however, chorionic invasion may occur and accentuate the weakness of the scar or the overdistention may result in disruption of the scar.

The argument that a routine repeat section should be done as prophylaxis against uterine rupture is not absolutely valid. Review of literature will reveal many instances of rupture occurring before term. Swift reported a case of spontaneous rupture at three months' gestation following a classical section and an abdominal pregnancy. LaMariana, in 1932, found 24 cases rupturing before term—7 cases ruptured in the seventh month of pregnancy! (Table I.) A prophylactic section, even when the rare first trimester rupture is eliminated, must have been done by the seventh month if all of the uterine ruptures were to have been prevented—an obviously absurd statement, as was pointed out by Karl Wilson in 1926.

TABLE I. TIME OF UTERINE RUPTURE
REVIEW OF LITERATURE BY PETER LAMARIANA (1933)

Full term	110
Eight months	12
Seven months	7
Eight and one-half months	5
Eleven months	1
Total	135

VAGINAL DELIVERY FOLLOWING CESAREAN SECTION*

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WHETHER or not a patient with a history of cesarean section should be permitted an attempt at vaginal delivery is controversial. Committed to the dictum "once a cesarean section, always a cesarean section," as advocated by Couvelaire, Breitsen and Marioton, are such modern authorities as Dieckmann, Seeley and Bill. On the other hand, Stander, Waters, Wilson and McLane and Phaneuf permit vaginal delivery in properly selected patients. We hold with the latter group.

The entire decision as to the management of a previously sectioned patient rests on the evaluation of the uterine scar. Experimental investigations and studies of excised cesarean section scars and excised uteri containing such scar have shown that healing is effected by fibroblastic proliferation. According to Schwarz, Paddock and Bostnick:

"... healing process takes place chiefly by proliferation of fibroblasts along the line of incision entering the spaces between the adjacent muscle bundles. As the scar shrinks, this becomes less perceptible and it is difficult to demonstrate the line of incision with ordinary hemotoxylin-eosin stain after two weeks' period. Special stains, namely van Gieson, bring out this differentiation.

"... In uteri removed after previous cesarean section, the scar is frequently imperceptible but in many instances, increased connective tissue can be demonstrated. The reason that the scar is imperceptible is due to the marked shrinkage of the newly developed connective tissue and the fact that it branches off in between the muscle bundles along the line of incision. If the suturing has been done well, the muscle edges are in close apposition, which necessitates only a narrow line of healing. As this shrinkage takes place, the normal relationship of smooth muscle and connective tissue, as occurs in normal pattern of the non-injured uterus, is similar."

The strength of such well-healed scar is even greater than the muscle itself. This has been evidenced both experimentally and clinically. Mason and Williams, in 1910, took uterine muscle strips containing cesarean section scar (from guinea-pigs and cats) and subjected them to progressive stretching by means of increasing weights. The site of the resulting rupture was always in the muscle and not in the scar! Clinical reports of rupture through the muscular portion of the gravid uterus while the scar remained intact indicate the relative strength of the two tissues.

Defective scars, however, are weak. From the ideal, firmly united, strong scar described above, there are all gradations to a scar consisting only of peritoneum and decidua. The two principal causes of weak scar are infection and faulty surgical technique. Perfect coaptation may be prevented by leucocytic infiltration associated with more or less tissue necrosis. Wide, weak scar may

*Presented at a meeting of the Chicago Gynecological Society, Dec. 19, 1947.

TABLE VI. PARITY AT TIME OF SECTION

	i	ii	iii	iv	v
Section elsewhere, first vaginal delivery elsewhere	5	1	-	-	-
Section elsewhere, first vaginal delivery at Lewis Memorial Maternity Hospital	15	-	-	-	-
Section and first vaginal delivery at Lewis Memorial Maternity Hospital	17	7	3	1	2
Total	37	8	3	1	2

TABLE VII. NUMBER OF DELIVERIES FOLLOWING SECTION

	1	2	3	4	5	Total
Section and first vaginal delivery elsewhere	-	2	2	1*	1	6
Section elsewhere, first vaginal delivery at Lewis Memorial Maternity Hospital	11	1	3†	-	-	15
Section and first vaginal delivery at Lewis Memorial Maternity Hospital	17	10‡	1	2	-	20
Total	28	13	6	3	1	51

*Section—forceps—forceps—pubiotomy—spontaneous.

†Section—version and extraction—forceps—section (1 case).

‡Section—forceps and version and extraction for twins—low cervical section (1 case).

TABLE VIII. TYPES OF DELIVERIES FOLLOWING SECTION

	1ST	2ND	3RD	4TH	5TH	TOTAL
Spontaneous	28	17	8	4	1	58
Forceps:						
Not specified	2	2	-	-	-	4
Low	16	-	-	-	-	16
Mid	2	-	-	-	-	2
Breech extractions	2	2	-	-	-	4
Version and extraction	1	-	-	-	-	1
Pubiotomy	-	-	1	-	-	1
Subsequent section	-	1	1	-	-	2
Total	51	22	10	4	1	88
Twins	3	1	1	-	-	5

Since 6 of the 51 patients had both the cesarean section and the first subsequent vaginal delivery performed elsewhere, only the remaining 45 patients had "trial of labor" which could be evaluated. Of these 45 patients, 31 had had the operation at the time of first pregnancy (therefore, as a primipara and to be referred to as primipara section group) and 14, after the first parity (therefore, as a multipara and to be referred to as multipara section group). The duration of labor for the first vaginal delivery following a section for the two types of patients is shown in Table IX. Comparative birth weight studies (Table X) reveal that 17 primiparous section and 6 multiparous section patients were delivered of a larger infant at the subsequent vaginal delivery than at the section delivery. This is important from two standpoints: first, that the clinical impression of disproportion may be erroneous, and, second, that overdistention per se does not cause weak scar as has been discussed already. Reference to Table XI shows 9 patients sectioned for "disproportion." Five of such patients had larger infants at the subsequent vaginal delivery and two additional patients had twins with their first pregnancy following the section.

TABLE IX. DURATION OF FIRST STAGE OF LABOR IN FIRST VAGINAL DELIVERY AFTER SECTION

SECTION AT: (HOURS)	0-2	2-4	4-6	6-9	9-12	12-18	18-24	24-36	OVER 36	MAXIMUM	MINIMUM
Primiparas	1	5	6	3	8	3	1	2	2	56 hours 15 minutes	1 hour 21 minutes
Multiparas	0	6	2	2	1	2	1	0	0	23 hours 9 minutes	2 hours 35 minutes

In the light of above knowledge regarding wound healing, strength of well-healed cesarean scar, and the causes of weak scar, a trial of labor does not seem contraindicated in selected patients. With the view toward proper evaluation of the risk involved, the charts of all patients delivered at Lewis Memorial Maternity Hospital between Jan. 1, 1931, and Nov. 1, 1947, were reviewed. The general statistical data are presented in Table II. The total number of patients with a history of cesarean section (or sections), whether performed at Lewis Memorial Maternity Hospital or elsewhere, was 385. Of this 385, 106 were subjected to one or more repeat section and 51 were successfully delivered via the vaginal route (Table III). Thus, 32.4 per cent of the 157 patients with a history of section at the preceding pregnancy were so delivered. Of the 51 patients, 45 were delivered of their first pregnancy following the cesarean section at the Lewis Memorial Maternity Hospital (as shown in Tables V and VI). There were 88 deliveries in the 51 patients. In Table VII is shown the distribution according to the number of deliveries subsequent to the section, while the number and the types of deliveries are shown in Table VIII.

TABLE II. GENERAL STATISTICS, JAN. 1, 1931, TO NOV. 1, 1947

Total number of patients registered		23,989
Total number of deliveries		31,368
Total number of cesarean sections		466
Classical type	291	} 456
Low cervical type	165	
Porro type		5
Posthumous type		5
Total number of ruptured uteri		5
With section history	3	
Without section history	2	
Abdominal pregnancy		1
Pubiotomies		5
Craniotomy		1
Maternal deaths		53
Following section	11	
Without section	42	

TABLE III. NUMBER OF SECTIONED PATIENTS (POSTHUMOUS SECTIONS NOT INCLUDED)

Total number with history of cesarean section		385
1 section (including Porro in 4)	279 (72.5 per cent)	
2 sections (including Porro in 1)	75 (19.5 per cent) *	
3 sections	24 (6.2 per cent)	
4 sections	5 (1.3 per cent)	
5 sections	2 (0.5 per cent)	
Total number delivering vaginally after a section		51
or 13.2 per cent of all patients with section		
or 32.4 per cent of all patients with <i>previous</i> section.		

*Includes 2 patients with vaginal deliveries between first and second section and 3 cases by ruptured uteri.

TABLE IV. PARITY AT TIME OF FIRST SECTION (POSTHUMOUS SECTIONS NOT INCLUDED)

Para	i	ii	iii	iv	v	vi	vii	viii	ix	x
Number	260	54	25	19	10	7	5	2	1	2
Per cent	67.5	14.0	6.5	4.9	2.6	1.8	1.3	0.5	0.2	0.5

TABLE V. PLACE OF SECTION AND VAGINAL DELIVERY

Section elsewhere, first vaginal delivery elsewhere	6
Section elsewhere, first vaginal delivery at L. M. M. H.	15
Section and first vaginal delivery at L.M.M.H.	30
Total	51

being reached at 11.0 cm. and a history of preceding section delivery elsewhere, a repeat section was performed. The uterus was found ruptured. The intact bag of waters was protruding through the rent. A live 7 pound, 6 ounce infant was delivered. The edges of the ruptured wound were found completely scarred and there was no bleeding. The scarred edges were excised and the uterus was closed in 4 layers. The postoperative course was completely afebrile and uneventful.

CASE 3.—No. 22,537, 32 years old, para i, gravida ii, with a cesarean section delivery of a 9-pound stillbirth with the first pregnancy in 1945. The operation was done at another hospital but the patient stated that there had been preoperative hemorrhage.

With her second pregnancy, in 1947, she was admitted 10 days before the expected date of confinement with a history of labor pain and a spontaneous rupture of the bag of waters. Preoperative diagnosis of "impending rupture of the uterus" was made on the basis of strong labor pains and marked tenderness over the former incision site. Laparotomy revealed an early rupture of the lower segment, although it was still covered by an intact peritoneum. A live term fetus was delivered and the uterine rent closed. The postoperative course was uneventful and afebrile.

Thus, in the 3 cases of ruptured uteri, there was no maternal mortality or "morbidity" and the fetal salvage was 67 per cent.

The fetal outcome in the 86 successful vaginal deliveries were: 5 sets of twins, 3 fetal deaths, and one 3 pound, 3 ounce, premature infant who survived! Of the 3 deaths, one infant was delivered vaginally *because of the diagnosis of intrauterine death* which occurred 5 days prior to the scheduled date for the repeat section. The second fetal death case was a 5 pound, 2 ounce hydrops fetalis delivered 8 weeks prematurely. This mother had been sectioned at the preceding pregnancy, which was her fifth, ten weeks before the expected date of confinement because of bleeding, only to have a 3 pound, 6 ounce fetal hydrops. The third fetal fatality occurred in a ten weeks premature 3 pound, 11½ ounce infant who survived only ten hours. The section delivery preceding this delivery in this mother had been performed elsewhere and the weight in that fetus had been 3 pounds. Thus all three deaths were nonpreventable.

TABLE XIII. BIRTH WEIGHTS AT VAGINAL DELIVERIES FOLLOWING SECTION DELIVERY

3-4 lb.	4-5 lb.	5-6 lb.	6-7 lb.	7-8 lb.	8-9 lb.	9-10 lb.	10-11 lb.	Twins
2	0	2	13	29	22	10	3	5

. Discussion

The proponents of routine repeat section will probably point out that an incidence of three ruptures in 157 patients, particularly of the silent kind illustrated by Case 2, not only justify *but indicate* prophylactic section. They will state that it is impossible to determine which patient is going to suffer a ruptured uterus. Cases of rupture occurring after an interval of vaginal delivery are cited as evidence. Yet, the same worker will agree that an attempt at vaginal delivery is indicated when the fetus is known to be dead. This seems inconsistent. The maternal risk in a ruptured uterus is the same regardless of the state of the fetus.

The mortality following a rupture of cesarean scar is estimated to be around 10 to 15 per cent. Burkons reported an incidence of 11 per cent and stated that the obstetrician who favors vaginal delivery following a section assumes less risk than if he routinely resectioned all patients. His logic was as follows: the average incidence of rupture following classical section is 4 per cent, of this, 11 per cent may be expected to die—an incidence of 0.44 per cent

TABLE X. CASES WITH GREATER BIRTH WEIGHT AT VAGINAL DELIVERY THAN AT SECTION DELIVERY

SECTION AT:	0-7 oz.	8-15 oz.	1-2 lb.	2-3 lb.	3-4 lb.	4-5 lb.	OVER 5 lb.	TWINS
Primiparas	3	3	7	0	2	1	1	4
Multiparas	2	0	3	1	0	0	0	1

TABLE XI. INDICATIONS FOR THE SECTION

Placenta previa	11
Abruptio placentae	4
Toxemias of pregnancy	6
Eclampsia	1
Pre-eclampsia	4
" toxemia "	1
Toxemia and antepartum bleeding	1
Disproportion	9
Prolonged labor	4
"Weak" indications	4
Desire for live child	1
Double vagina	1
Old 3° laceration	1
Compound presentation, prolapsed foot	1
Not determinable (sectioned elsewhere)	12
Total	51

The type of cesarean section preceding the vaginal delivery is shown in Table XII. Since 1942, the low cervical section has been employed almost exclusively and the transverse incision generally favored over the vertical one. The number of successful vaginal deliveries following the classical section, however, seem to indicate that the site of incision does not contraindicate "a trial of labor." There have been, however, three instances of uterine rupture in patients with history of section. Because of their importance, the three cases are abstracted here:

TABLE XII. TYPES OF SECTION PRECEDING VAGINAL DELIVERY

Sectioned elsewhere (probably classical)	22	} 46
Classical section at Lewis Memorial Maternity Hospital	24	
Low cervical section at Lewis Memorial Maternity Hospital		5
Transverse uterine incision	2	
Vertical uterine incision	3	

CASE 1.—No. 8161, 40 years old, para i, gravida ii. First pregnancy in 1934 was terminated at the 30th week by classical section for "eclampsia." Fetal weight was 3 pounds 13 ounces. Closure was in 4 layers. Postoperative course was uneventful and afebrile.

With her second pregnancy, 1936, she was admitted 13 days prior to the expected date of confinement, in a state of shock. The accompanying relatives stated that the patient suffered sudden onset of pain which rapidly became continuous in nature. She was treated for her shock. After two days, she was operated upon and found to have a ruptured uterus with complete extrusion of the intact placenta and bag of waters out into the peritoneal cavity. The infant was dead. The uterus was well contracted but was removed subtotally. The convalescence was uneventful and afebrile.

CASE 2.—No. 15,521, 23 years old, para i, gravida ii. First pregnancy occurred in 1937 and she was delivered by cesarean section at an outside hospital. The indication was not given but the fetal birth weight was 9 pounds.

With her second pregnancy, 1939, she was admitted at term with a history of onset of mild labor. In view of our finding of "justo minor" pelvis with the false promontory

reported uterine ruptures occurring following cesarean section but with normal deliveries in the interval between. Dieckmann mentions a case following an interval of two vaginal deliveries. On the other hand, Mason and Williams (1910) and Lemeland and Lacomme (1933) have reported cases with vaginal deliveries following three preceding sections. In general, the greater the number of vaginal deliveries, the less likelihood is there of rupture. The danger, however, is always present, so that every gravida with a history of cesarean section must be observed carefully at all times and particularly in the last trimester. All complaints of vague abdominal pain and tenderness must be carefully evaluated so that when rupture does occur or can be anticipated, prompt appropriate measures may be taken (as the treatment of shock in our first case, and the prompt intervention in the third case). Under such regime, the maternal risk may be kept at a minimum consistent with the justification for an attempt at vaginal delivery.

Summary

The literature has been reviewed regarding the wound healing, the causes of weak scar, and the risks involved in ruptured uteri following cesarean section. There seems to be definite indication for an attempt vaginal delivery under certain circumstances as outlined.

The 18 years' survey at the Lewis Memorial Maternity Hospital revealed that 51 (or 32.4 per cent) of the 157 patients with a history of cesarean section were successfully delivered via the vaginal route. The incidence of ruptured uteri was three (or 1.8 per cent) *but not in the ones subjected to a trial of labor*. There was no maternal mortality or "morbidity" following the rupture. The fetal salvage was 67 per cent. In 37 out of the 51 vaginal delivery patients, the cesarean section had been done at the time of primiparity; in the remaining 14, one to four vaginal deliveries preceded the section. The maximum and minimum duration of the first stage of labor in the first vaginal delivery following the section were 56 hours 15 minutes and 1 hour, 21 minutes, respectively, in patients sectioned as primiparas; and 23 hours, 9 minutes, and 2 hours, 35 minutes, respectively, for patients sectioned as multiparas. Seventeen primiparous section patients and six multiparous section patients were delivered of a larger infant at the subsequent vaginal delivery than the original section delivery. There were 86 vaginal deliveries following the 51 section deliveries. The fetal deaths were 3—all nonpreventable (an intrauterine death before labor, an 8-weeks-premature hydrops fetalis and 10-weeks-premature 3 pound, 11½ ounce infant).

The danger of ruptured uteri complicating an attempt vaginal delivery is admitted and discussed.

Conclusion

A trial of labor seems indicated as the management of choice in a certain number of properly evaluated patients when supervised by a competent obstetrician in a hospital equipped to meet all emergencies. The significance of successful vaginal delivery following a cesarean section has been stressed. Thus, the old dictum "Once a cesarean section, always a cesarean section" should be changed to "Once a cesarean section, NOT NECESSARILY always a cesarean section."

of the original number, whereas, the basic mortality in resection cases as reported by Skeel and Jordan, quoting Burkons, is 1 to 2 per cent. McLane found no uterine rupture and no maternal mortality in his series of 43 cases. Duckering, of Stander's clinic, reported eight cases of ruptured uteri in previously sectioned patients with no maternal fatality. She attributes this to the careful observation and prompt treatment. We had no mortality in our three ruptured uteri.

There is little doubt that the maternal risk in a rupture through the old section scar is less than that resulting from ruptured uteri occurring in patients without such scar. Burkons found shock present in only two of the eighteen rupture patients with section scar while shock was the prominent condition in 23 of the 27 uterine ruptures in patients without the scar. It seems logical, therefore, that certain conditions indicate a "trial of labor" as the management of choice in certain select patients. This management, of course, must be under an experienced, well-qualified obstetrician at a hospital equipped to meet all emergencies. These conditions are:

1. *Early Engagement of the Presenting Parts.*—This condition facilitates evaluation of the cervical status, particularly during labor. In 10 of the 45 patients, engagement occurred three to five weeks before the onset of labor.

2. *History of Vaginal Deliveries Preceding the Section Delivery.*—The comparatively lighter and shorter labor of each succeeding pregnancy indicates the relative ease of effacement and dilatation of the cervix. The greater the number of vaginal deliveries preceding the section, the easier and shorter may be the expected labor. Table IX confirms this impression.

3. *Diagnosis of Death or Monstrosity in Utero.*—Uniformity of opinion is approached regarding this indication. In one of our patients scheduled to have repeat section on basis of previous section by unknown operator indication, intrauterine fetal death was diagnosed five days prior to the date of scheduled operation. She was, therefore, permitted to go into spontaneous labor and delivered of a 7 pound 11 ounce macerated stillbirth after twelve hours of labor.

4. *Reasonable Assurance of Well-Healed Scar.*—As has been discussed, a well-healed, strong scar may be reasonably expected when the surgical technique is known to be good and the postoperative course uneventful and afebrile (i.e., free of infection). This, plus the absence of the original indication for the section, will indicate a trial of labor.

The significance of successful vaginal delivery subsequent to a section delivery is obvious. Once a patient has had such a delivery, the contraindication to a careful "trial of labor" is almost completely removed. Even the most ardent advocate of repeat section will concede that an attempt is justifiable with all subsequent pregnancies (for that patient). This becomes of greatest importance when it is realized that the majority of the first sections are performed on primiparous patients (Tables IV and VI), how often operations are done on erroneous indications (Table XI) and the fact that some authorities attach so much danger to repeated sections that routine sterilization is practiced after the second or third cesarean section! A successful vaginal delivery, then, at least partly corrects what Kennedy refers to as "tragedies of the uterine incision incident to the cesarean section."

The danger of uterine rupture occurring during labor is admitted. We have had three in our 157 patients. Furthermore, a successful vaginal delivery does not guarantee against future rupture. Fava, Casagrand, and others have

small. The authors do not state their results in the 106 patients who had subsequent sections. A comparison would be interesting. Since sterilization has not been permitted in their hospital, I should think they would have a fairly large series with more than three repeat sections. What are their results in these cases?

When one eliminates those patients (1) who have had cesarean sections for frank disproportion or after a test of labor; (2) those who are known to have had a febrile post-operative course; (3) those who were operated upon elsewhere, for whatever cause; (4) those who were operated upon through the site of a low-lying placenta; (5) and those who have uterine myomas or other pelvic tumors, the number who will be eligible for a trial labor will be relatively small.

Too many of us have arbitrarily taken the easy way and done repeat sections without considering vaginal delivery. It has been our custom to operate on these women about a week before their expected date of confinement, and if they go into labor spontaneously before this time, we hurry them to the operating room. Thus, our women have not been permitted a trial labor. Personally, I have delivered only two women vaginally after cesarean section. One of these, a para ii, entered the hospital in labor with a well-engaged head, a soft cervix dilated to 5 cm. She was allowed to continue in labor and delivered easily in a few hours with the aid of outlet forceps. The other had delivered twice vaginally, prior to cesarean section for central placenta previa. She refused a second section and delivered successfully from below. I believe that if more of my patients were given a trial labor, many of them would accomplish the same thing.

From the authors' experience, I agree that the old dictum, "Once a cesarean, always a cesarean," is not necessarily correct. With careful selection of cases and careful observation in a well-equipped maternity hospital, it seems that a trial labor is occasionally justified. The authors speak of "trial labor" and I assume from this that not all of their women are allowed to finish labor. How many were eventually delivered by cesarean after a trial? I would still be afraid to allow a woman to continue through labor when progress stops for whatever reason. They have only mentioned watching for signs of rupture through the previous site of the uterine incision as an indication for section. Should some dilatation and effacement, and engagement, be found on examination prior to the onset of labor, then the outlook for vaginal delivery should be anticipated as favorable. Should a woman who has never previously dilated her cervix, enter the hospital in labor, with no dilatation, no effacement, and no engagement, it would be against my judgment to allow trial labor for too long.

DR. HUGO BAUM.—As a general statement, "once a cesarean section, not necessarily always a cesarean section" does not require debate. Probably every clinic has had the experience of admitting an obstetric patient, previously sectioned, but this time presenting herself near the end of the second stage of a precipitous labor and easily delivering through the birth canal. Drs. Schmitz and Baba have shown that in a well-equipped, well-staffed hospital many more previously sectioned patients, carefully selected, can be delivered through the birth canal.

Rightly, all papers on vaginal delivery following cesarean section emphasize the condition of the uterine scar. Wound healing naturally depends upon the care with which margins of an incision are approximated and upon the absence of infection. However, there is another factor not easily evaluated but equally, if not more, important which has not been mentioned and is usually not considered. This factor might be termed the general nutritional health status of the patient. This factor probably accounts for defective scars seen in those patients who have received the best of surgical technique and whose convalescences have been afebrile.

Since the ultimate factor determining whether or not a patient, one previously sectioned, can subsequently be delivered through the birth canal depends upon the uterine scar, it is unfortunate that we are unable, as on an automobile, to lift the hood and inspect the scar. Instead, we must depend upon unreliable palpation and upon the subjective symptoms of tenderness and pain over the site of the previous incision. Individual susceptibility to pain and anxiety are not measurable and thus our estimation of the scar can only be an impression.

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Discussion

DR. R. M. GRIER.—The authors are to be commended for their courage in re-evaluating the risks involved in allowing vaginal delivery after a previous cesarean section. There are too few comparable reports in the literature. They have given us a very thorough study of the arguments for and against such management. They have considered for this study 157 women; though they have had many more cesarean operations at the Lewis Memorial Maternity Hospital, I assume, these are all that were subsequently delivered by them. Of these, less than a third, or 51, were given trial labor. Since six of these were delivered elsewhere, they have not been considered. This leaves 45 women who have been observed by the authors. Twenty-eight were delivered once vaginally. Seventeen of the twenty-eight had subsequent pregnancies and two of these were delivered by section. Therefore, only 15 women were delivered more than twice in this manner. Just four more infants were born than would have been possible had these women been sterilized following a third cesarean. It has been our rule to recommend interruption of the tubes following a third operation. I have not yet lost a patient following repeat cesarean, but my series of cases is relatively

maternal mortality after cesarean section was 0.4 per cent but that their maternal mortality from cesarean section is 0.9 per cent. Therefore it would be better to subject the patient to a test of labor even though the uterus might rupture. Obviously these statistics are misleading.

The authors report vaginal delivery of 51 out of a possible 157 patients who had had previous cesarean section. If vaginal delivery can be carried out so safely, why were not the other 106 patients also subjected to vaginal delivery? These statistics have been collected over a period of 18 years, obviously *after* the deliveries had occurred. Are no repeat sections now performed by the authors? Would they want their wives or daughters to have a test labor after cesarean section, and if so, would they be willing for them to labor 23 to 56 hours? It is not the doctor's life they are gambling with, it is the life of the patient and her baby and are we justified in such a gamble? No one can foretell which uterus will rupture. There are no characteristic symptoms and signs of imminent rupture of the uterus.

There is an irreducible mortality associated with reproduction. We have had over 49,000 deliveries (1,000 Gm. or more) in the hospital from 1931 to June 30, 1947, with a total uncorrected maternal mortality of 70 or 0.14 per cent. If we correct for approximately two-thirds of the deaths which had preventable factors, the maternal mortality is then approximately 0.05 per cent. We have in this same period performed 2,333 cesarean sections with a total mortality of 11, or 0.47 per cent; obviously higher, but many more of these women would have died with vaginal delivery. We have included one woman who died at home three months after delivery from an abdominal abscess resulting from the operation. Of the 11 deaths, two were due to tuberculous meningitis, one was on a moribund eclamptic, six were probably preventable and one possibly had preventable factors. In other words, there was only one nonavoidable death, due to pulmonary embolism. Since July 1, 1942, we have performed over 860 consecutive cesarean sections, without a single maternal death. We have had some seriously sick patients who required intensive treatment but they have survived and have not been left crippled. We believe the patient is entitled to that treatment which yields the lowest maternal and fetal mortality, morbidity, and lack of injury to soft parts.

Our uncorrected stillbirth and neonatal mortality for all deliveries, from 1941 to 1946, of fetuses weighing 1,000 Gm. or more, is 2.5 per cent. The corrected mortality for all vaginal deliveries, from 1941 to 1943, of fetuses weighing 1,500 Gm. and more due to the delivery, *per se*, is 0.7 per cent. I am positive that our corrected fetal mortality for elective cesarean section at 37 or more weeks' gestation is less than 0.3 per cent. Compare this mortality with that for vaginal delivery and with that (33 to 100 per cent) for a possible rupture of the uterus. There is no question but that the baby has a better chance by an elective cesarean section than by vaginal delivery.

I think the conclusion of the authors that vaginal delivery after cesarean section is a safe procedure, even though they carried it out in only a third of their cases, is wrong and dangerous because doctors will try it and will have an increased mortality. There should be less criticism of the doctor who performs an occasional questionably unnecessary cesarean section and increased caustic criticism of the doctor who delivers vaginally when he should have performed a cesarean section or who waits too long before performing the operation and ends with either a dead baby, a dead mother, or both. There is no excuse for this type of obstetrics. It belongs to the past.

Once a cesarean section, always a cesarean section, should be one of the doctor's commandments. Another commandment is: cesarean section and cesarean-hysterectomy are elective procedures for the treatment of selected cases and not a last-minute attempt to empty the uterus when vaginal delivery has failed.

DR. J. P. GREENHILL.—About 25 years ago I wrote a short paper with the title, "Once a Cesarean Section, Always a Cesarean Section, an Untruth." I wrote it because in one year four women were delivered vaginally at the Chicago Lying-in Hospital who had had previous cesarean sections because of disproportion. Each of the four babies born through the vagina weighed more than the baby delivered by cesarean section.

I, personally, have watched selected patients, during trials of labor, develop symptoms suggestive of thin scars, only at section to find a firm union which probably would have withstood labor, and again have observed in other patients, at the time of repeat section, scars which were so thin that definite diastasis existed, which gave no symptoms and probably would not have given symptoms unless the patients had been allowed to progress in labor and had ruptured the uterus.

In the five years, 1942 through 1946, 6,545 patients have been delivered at the Presbyterian Hospital of Chicago. There have been 273 sections, an incidence of 4.1 per cent; of these, 115 were repeat sections. There has been one cesarean section death, a primigravida, giving a mortality rate of 0.36 per cent. Of the 115 repeat sections, there was one patient who, at the time of her second cesarean, had beginning separation of the lower end of the uterine scar and a small hematoma forming beneath the bladder reflection. Four patients of the 6,545 had vaginal deliveries following previous cesarean section. Three of these had their first pregnancy delivered by cesarean section and their labors were typically primiparous. The fourth had first a normal delivery, then a cesarean section for placenta previa, and then a vaginal delivery. All four had the second stage terminated by low forceps. In the report read tonight, there is a record of one patient, not delivered at Lewis Memorial Hospital, on whom a pubiotomy was performed to permit vaginal delivery following cesarean section. Such a procedure cannot be justified today. Version and extraction delivery of a twin pregnancy is not without danger of a ruptured uterus even when the babies are small.

I agree "once a cesarean section, not necessarily always a cesarean section," but I hesitate to consider the tragedies which might result in hospitals where vaginal deliveries following cesarean section are attempted, which are not prepared to make careful selection of patients to be given a trial of labor and are not prepared to cope with the ruptured uteri which they will encounter. This next statement may seem unnecessary, but maternal deaths prove otherwise. Having compatible blood available, ready for administration, is as important as having the operating room ready to handle the emergency, for treatment of accompanying shock must precede surgery.

DR. W. J. DIECKMANN.—I do not feel that the authors have offered any positive proof that vaginal delivery, after cesarean section, is safer for mother and baby than a repeat elective section.

They state that if you practice repeat cesarean section, then you must perform the operation at 30 weeks because ruptures have occurred at this time. This is very rare and, furthermore, uteri have ruptured at 12 weeks. In other words, the authors seem to suggest that these women should not have become pregnant.

They also state that craniotomy for the dead baby is not desirable. Perhaps they are correct, but experience indicates that many uteri rupture during the second stage. We try to prevent this by craniotomy at 7 to 8 cm. dilatation. We dislike subjecting the patient to the increased risk, small as it is, of section for a dead baby.

I question the statement that scar tissue is stronger than the original tissue. I do not believe that the maternal risk is less in rupture through the cesarean scar than that involved in rupture without a scar.

Only three ruptures of the uterus in 157 patients with cesarean scars in 18 years, and no maternal mortality or morbidity in these three patients is an excellent record.

We have a high morbidity in all of our uterine ruptures where fetus and/or placenta is extruded into the abdomen. We have had no mortality from rupture in over 740 patients who have had a previous section. I would certainly not want to be responsible for a test of labor in one patient per week (our average) with a uterine scar.

Vaginal delivery after cesarean section carries an increased risk. The reports of rupture of the uterus after cesarean section from the obstetric services at Harvard, Cornell, Hopkins, Western Reserve, Tulane, Loyola University, and our service reveal a maternal mortality of from none to 42 per cent and a fetal mortality as high as 100 per cent. All services report some deaths. Delfs, reporting the Hopkins' statistics, states that the risk of

THE EFFECTS OF VARIOUS ESTROGENIC PREPARATIONS

II. Changes in the Vaginal Mucosa and General Status of Climacteric Women Following the Injection of Aqueous Suspensions of Estrone and Estradiol

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THE standardization of estrogenic material for use in human beings exists as a problem of no mean proportions. Methods of assay have varied from observer to observer and from manufacturer to manufacturer. These statements are applicable to the two active forms of ovarian follicular hormone known to be physiologically present in man, estradiol and estrone. Despite the fact that both of these have been isolated in pure form and carefully assayed in small laboratory animals, attempts to express the dosage of one in terms of the other, even on a weight-for-weight basis, have resulted in widely variant recommendations regarding their use in human beings.

In order to avoid some of the difficulties into which any clinical comparison may fall, the present study was planned so that:

1. Estradiol and estrone were tested at two levels of dosage for each individual subject.
2. Water, as a menstruum for estrogenic material, could be appraised.
3. Subjects were selected whose past record was well known or had been followed for a considerable period of time.
4. An appraisal of the influence of the estrogen upon clinical manifestations could be made separately and independently of the changes taking place in the vaginal smear.
5. No regular sequence of treatment was followed; that is, in one subject, one preparation and dosage level were used first, in a second, the order might be reversed, and so forth; except for the fact that estradiol in 1 mg. doses was never used first.
6. The priming effects of previous doses of estrogen were minimized.

Material and Methods

A. Preparations.—

The four preparations employed in this study were aqueous suspensions containing per c.c. 2 mg. estrone, and 0.5 mg. estradiol, administered in 1 c.c. and 2 c.c. doses, respectively.* Watery suspensions were employed in the belief that the insoluble state of the estrogenic material might make for a slower absorption and more prolonged effect. In a few instances, the site of the injection of the watery suspension was sore, as compared with the absence of distress when oily preparations were used.

*We gratefully acknowledge our indebtedness to Dr. E. W. Henderson, of the Schering Corporation, Bloomfield, N. J., for the preparations used in this study.

Dr. Baba mentioned the work of Dr. Schwarz on the regeneration of scars following classical cesarean section. In 1929, Bloom and I reported a study of the scars which followed cervical cesarean section. It was amazing what some scars withstood because in some instances the scars were extremely thin and irregular, and yet they did not rupture during active labor. It did not make much difference who the operator was. There seemed to be some evidence that the better scars were the ones closed with interrupted sutures.

I agree with Dr. Dieckmann concerning the wisdom of performing repeat cesarean sections in nearly all cases, because we cannot be certain that a rupture will not occur during labor. After classic cesarean section, there is the decided risk of rupture of the uterus during pregnancy, in addition to the danger of rupture during labor.

DR. SCHMITZ (Closing).—Relative to the remarks of Dr. Grier, I think that the reason there were any repeat sections in this relatively small number of cases which he alluded to was due to the fact that there was definite indication for repeat section in that group. Therefore, there would be fewer cases that we thought were ideal for attempt at vaginal delivery. All these patients, as we stated in the paper, came to the hospital with the head well down in the pelvis, the cervix effaced and dilated. A few cases of prolonged labor were found. We have all seen patients who have come in with effacement and partially dilated cervix, giving us the hope of a very rapid and uncomplicated delivery, then developing a uterine inertia from weak and unsatisfactory pains lasting many hours, during which time we spend many unhappy minutes watching them and fearing the possibility of rupture. From our observations in this group of patients, we feel that by carefully watching the patient, sedating the patient, and being ready at the least indication to do a repeat cesarean section that we have not added any risk to the mother.

The pubiotomy that was done was done many years ago, as were the version and extraction and some of the other procedures which we would certainly not condone. Inasmuch as we viewed the records of the hospital since its inception we thought it only fair that we include these in the study, so that the conclusion would be either for or against having them done. In the remaining patients who had repeat sections, and this was published in our study on cesarean section, there were no deaths.

I cannot differ too much with Dr. Dieckmann. I respect his experience and his judgment, but it did seem to us in watching these cases that if the conditions which we have set forth were present there was no greater risk for the mother in permitting her to deliver from below. We merely tried to bring out, in quoting other statistics, that rupture could occur at the time of elective cesarean section. If we were to avoid all danger, then we must do our sections shortly after or at time of term. I do not believe this study is going to influence many people to attempt delivery from below. I believe it is something for us to discuss in a meeting of this type. We will try to evaluate it further and if, in the future, our results are not so good, we will be very willing to admit it and to agree with Dr. Dieckmann.

Result

A. Following an Injection of 2 Mg. of Estrone.—

1. *Objective* (Tables I and II, Fig. 1): In seven of twenty patients who received injections of 2 mg. estrone, there was no significant alteration of the vaginal secretion; in two the results were questionable. Eleven subjects showed definitive changes occurring between the 72nd and 168th hour following administration of the estrogen. The average lag-time* was 120 hours. The duration of the response ranged from 24 to 180 hours, with an average of 99 hours. The degree of estrogenic activity attained was one plus in 3, two plus in 4, three plus in 2, and four plus in 2 cases, respectively.

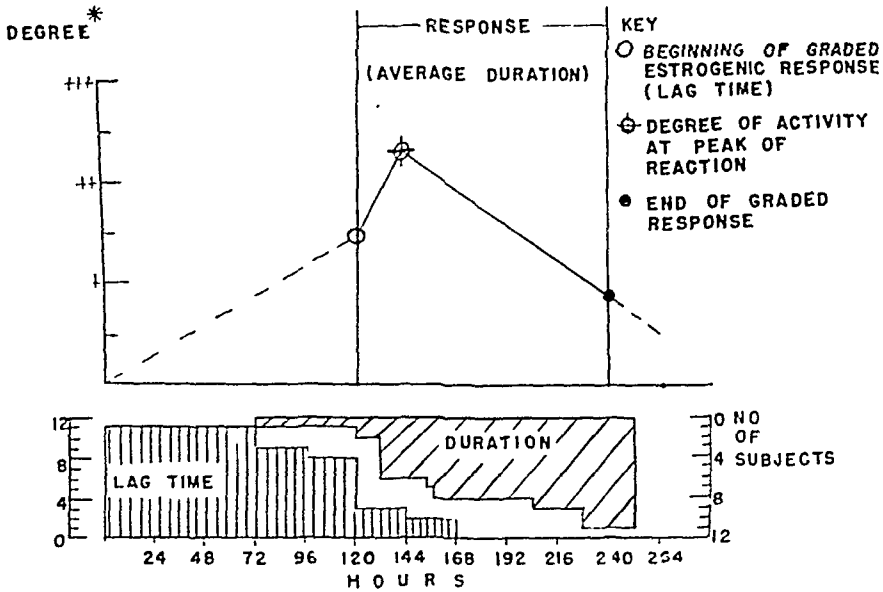


Fig. 1.—The averaged response of eleven subjects to a single injection of 2 mg. estrone.

*Degree + — 10 to 25% cornification of epithelial cells.
++ — 25 to 50% cornification of epithelial cells.
+++ — 50 to 75% cornification of epithelial cells.

TABLE I. DATA ON INDIVIDUAL CASES

CASE NO.	AGE	STATUS*	CASE NO.	AGE	STATUS
1a	54	M	13a	48	M
2a	41	SC	14a	52	M
3a	46	Me	15a	28	SC
4a	61	PM	16a	33	SC
5a	24	SC	17a	26	SC
6a	46	M	18a	37	SO
7a	22	RC	19a	27	SC
8a	41	SC	20a	53	SC
9a	45	SC	21a	41	SC
10a	42	SC	22a	46	SC
11a	52	M	23a	50	SC
12a	52	M			

*Status: M—Menopausal; PM—Postmenopausal; SC—Surgical Castrate; RC—Roentgen-ray Castrate; SO—Unilateral oophorectomy; Me—Menses persisting.

**“Lag-time” is defined as the time elapsing between the injection of the hormone and clear-cut evidence of estrogenic response in the vaginal secretion.

In so far as possible, each subject was utilized in the testing of each preparation, thus serving as her own control. In order to minimize the priming effect of preceding doses, an interval of three weeks or more was allowed to elapse between injections. A total of 80 such tests were made. The procedures relating to the taking of vaginal smears prior to therapy and daily thereafter, the staining of the smears, and the method of tabulating the observations have been previously described.¹ Approximately 1,100 vaginal smears have been examined in following the effects of 80 injections of hormone.

B. Subjects.—

Twenty-three women with complaints which were climacteric in character have been treated successively with one or more of the four estrogenic preparations. Fifteen of these women, ranging from 24 to 53 years of age, had been surgically castrated and four, from 48 to 54 years old, were menopausal.* One woman, 61 years old, although many years postmenopausal, had climacteric* symptoms. Another patient, aged 22 years, had been castrated by roentgen ray. One 46-year-old subject (3a) was menstruating regularly and another, aged 37 (18a), had had a hysterectomy and unilateral oophorectomy. Control smears on 3a showed a "normal" cyclic vaginal secretion. Case 18a was studied for three months prior to initiation of therapy. Smears taken daily over this period of time showed the typical changes observed in smears of normally menstruating women, with an ovulatory peak occurring on the fifteenth day of the cycle. Objective changes in these two cases could not be properly evaluated and are classified as questionable throughout.

In other isolated instances, data regarding alterations in the vaginal smear have been tabulated with reservations. Included here are some of the observations on patients 1a and 14a, who, following injection of 4 mg. estrone and 1 mg. estradiol, respectively, showed cytologic alterations too slight to grade and patients 7a, 14a, and 16a, whose smears, at the time of administration of 1 mg. estradiol, 4 mg. estrone, and 0.5 mg. estradiol, respectively, indicated residual hormonal activity. This was attributed by us to the preceding injections of estrogen in patients 7a and 16a and probably to endogenous hormone formation in 14a, who menstruated for three days about two weeks after her third injection, i.e., approximately sixteen days prior to the dose in question. Similarly, patient 1a had an apparently "normal" menstrual period ten days after an injection of 1 mg. estradiol. Smears prior to flow showed a marked estrogenic effect and observations made at this time are difficult to evaluate. Six weeks later, a second injection of 1 mg. estradiol was administered and daily smears thereafter did not alter from the controls.

C. Evaluation of Symptomatic Relief.—

The most frequent complaints encountered in this group of patients were nervousness, trembling, headaches, hot flashes, dizziness, palpitations, and sweating. A few women complained of fatigue. The difficulties attendant upon the initial grading of these symptoms are apparent. The attempt has been made, however, to evaluate the degree of relief reported by the individual patients following each injection. The subjective response to the therapy has been qualitatively estimated (Table IV).

*In the sense used throughout this report, the term menopausal has been used to designate all subjects whose menstruation had ceased within 3 years of the date of beginning the injections. In contradistinction, the climacterium refers to the syndrome of glandular imbalance in which ovarian disturbances play a major role and which commonly arises at the menopause, but may appear at any time in life from puberty onward.

mucosa was 101 hours. The duration of follicular response ranged from 72 to 192 hours, with an average of 110 hours. The degree of activity exhibited by these patients varied from one to three plus.

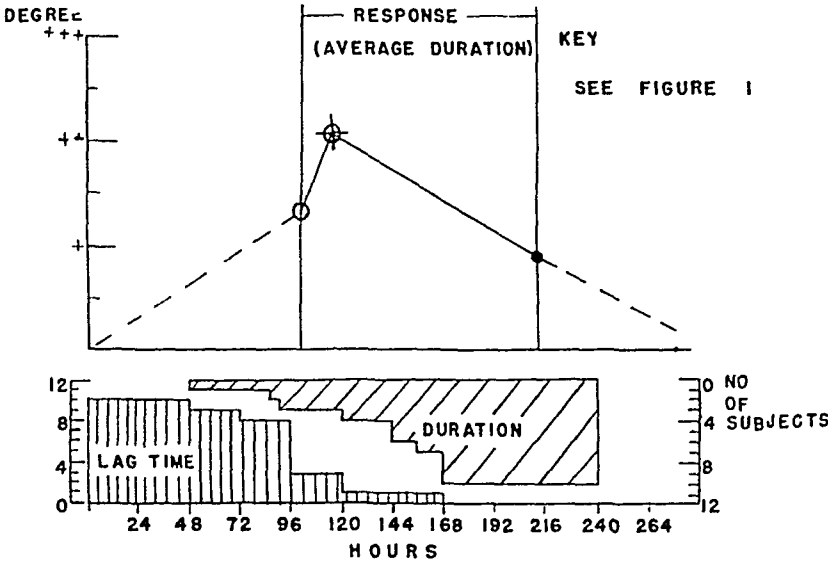


Fig. 2.—The averaged response of ten subjects to a single injection of 4 mg. estrone.

2. *Subjective* (Table IV): Complete relief of climacteric symptoms for a period of one week was noted by one woman whose vaginal smears indicated a high degree of cornification; marked relief for the same number of days was reported by a second subject (18a). Moderate improvement lasting from four to six days was experienced by three women, two of whom showed no alteration in the vaginal smear. Seven patients noted slight relief for approximately four days following the injection, although four of them gave no evidence, objectively, of hormonal stimulation. Four women whose smears showed definite follicular responses reported "questionable" improvement. Four subjects were not benefited at all: the vaginal smears of two in this group indicated an estrogenic response.

C. *Following Injection of 0.5 Mg. Estradiol.*—

1. *Objective* (Tables I and II, Fig. 3): Twenty-one women treated with injections of 0.5 mg. estradiol, responded positively, seven, not at all, and in three cases the results could not be evaluated. The number of hours between injection and the observation of a graded response in the vaginal mucosa of the eleven "positive" cases ranged from 24 to 168, with an average of 99 hours. The duration of estrogenic activity, measured by our standards, ranged from 24 to 192 hours, with an average of 110 hours. The degree of activity manifested varied from one to four plus.

2. *Subjective* (Table IV): Fifteen of the twenty-one women who received treatment with 0.5 mg. estradiol reported degrees of symptomatic relief varying from slight to marked; objectively, changes were observed in ten of this group. The vaginal smears of two patients who thought they might have been relieved showed follicular stimulation of the vaginal epithelium. In four cases there was no subjective response; the vaginal smears of only one of these four indicated some degree of hormonal activity (Table IV). The average duration of symptomatic improvement was five days.

TABLE II. THE AVERAGE LAG-TIME AND DURATION OF THE ESTROGENIC RESPONSE

THERAPY	SUBJECTS				RESPONSE			
	TOTAL TREATED	-	-	?	LAG-TIME (HOURS)		DURATION (HOURS)	
					RANGE	AVERAGE	RANGE	AVERAGE
Estrone 2 mg.	20	11	7	2	72-168	120	24-180	120
Estrone 4 mg.	21	10	7	4	48-168	101	72-192	110
Estradiol 0.5 mg.	21	11	7	3	24-168	99	24-192	110
Estradiol 1 mg.	18	10	3	5	48-144	91	48-168	104

2. *Subjective* (Table IV): Two of the seven women whose objective response was negative reported no improvement in subjective symptoms following administration of 2 mg. estrone; three were in doubt as to any relief and two experienced slight alleviation of their complaints. Eleven patients whose vaginal smears indicated varying degrees of estrogenic activity reported slight to complete symptomatic improvement over a three-to seven-day period. Of the two cases whose objective response could not be properly evaluated, one reported slight and the other no amelioration of climacteric disturbances.

TABLE III. THE ORDER OF EMPLOYMENT OF ESTROGENIC PREPARATIONS IN ALL CASES

PERPARATION		FIRST	SECOND	THIRD	FOURTH
Estrone	2 mg.	16	2	1	1
Estrone	4 mg.	1	15	3	2
Estradiol	0.5 mg.	6	3	12	0
Estradiol	1 mg.	0	3	2	13

TABLE IV. SUBJECTIVE IMPROVEMENT COMPARED WITH OBJECTIVE RESPONSE

SUB- JECTIVE RE- SPONSE	PREPARATIONS												TOTAL							
	ESTRONE 2 MG.				ESTRONE 4 MG.				ESTRADIOL 0.5 MG.				ESTRADIOL 1 MG.				SUB- JEC- TIVE RE- SPONSE	OB- JECTIVE RE- SPONSE		
	NO.	OBJECTIVE RESPONSE			NO.	OBJECTIVE RESPONSE			NO.	OBJECTIVE RESPONSE			NO.	OBJECTIVE RESPONSE						
		+	-	?		+	-	?		+	-	?		+	-	?				
Complete re- lief	1	1			1	1			1	1			1	1			4	3	1	
Marked re- lief					1		1		6	2	3	1	9	7	2		16	9	3	4
Moderate relief	2	2			3	1	2		3	1	1	1	2	1	1		10	5	3	2
Slight relief	4	2	1	1	7	2	4	1	4	3	1		3	1	1	1	18	8	7	3
Questionable relief	9	5	4		5	5			3	3			2	1	1		19	14	5	
No relief	4	1	2	1	4	1	1	2	4	1	2	1	1		1		13	3	5	5
Total	20	11	7	2	21	10	7	5	21	11	7	3	18	10	3	5	80	42	24	14

B. *Following Injection of 4 Mg. of Estrone.*—

1. *Objective* (Tables I and II, Fig. 2): Twenty-one tests were made with 4 mg. estrone on 20 patients. In ten instances the vaginal smears showed a positive estrogenic response; in four the findings were questionable, and in seven, unaltered. The range of lag-time was from 48 to 168 hours; the average period elapsing between injection and a graded stimulation of the vaginal

D. *Following Injection of 1 Mg. of Estradiol.*—

1. *Objective* (Tables I and II, Fig. 4): In 18 tests on 17 subjects, the administration of 1 mg. estradiol evoked an estrogenic vaginal response in ten instances, a doubtful one in five, and had no effect in three. The range of lag-time was from 48 to 144 hours, with an average of 91. The duration of the response varied from 48 to 168 hours and averaged 104. It reached a maximum degree of four plus in one, three plus in two, two plus in four, and one plus in three patients.

2. *Subjective* (Tables I and IV): Of the 17 women treated, one reported complete relief of all symptoms. Improvement was marked in nine patients, moderate in two, slight in two, and doubtful in two. One woman derived no noticeable benefit. Periods of relief varied from four to ten days.

Discussion

Following repeated frequent administration of estrogenic hormone, "withdrawal bleeding" in monkeys and human castrates is a common phenomenon, pointing to the cumulative effect of successive doses.³ We agree with Phelps² that the nature of any alteration in function or morphology of the genital tract is dependent upon the interaction of several factors, chief among which are the exogenous hormonal stimulus and the physiologic status of the subject in relation to its application. For instance, following estrogenic therapy in the menopausal woman, who has not menstruated for a considerable period of time, bleeding may occur in association with all the phenomena usually attendant upon her previously "normal" cycles. Here the exogenous hormone may have acted upon a pituitary-ovarian mechanism that had not become completely quiescent. The bleeding which occurred in patients 1a, 6a, and 14a of the present series is believed to have been of this type. In evaluating our results, we have attempted to eliminate in so far as possible any effects which might have been due to prior conditioning or "priming" of the subject, either as a result of her own or exogenous hormonal activity. Although the amount of hormone injected was small in each of the patients under study, frequently the appearance of smears taken fifteen to twenty-one days later was different from that of those obtained prior to therapy. Changes noted included an increase in the number of superficial cells with an occasional cornified cell, and a relative decrease in the number of elements of the deeper epithelial layers. Insofar as possible, we have allowed our subjects to return to a pretreatment status before administering an additional dose of estrogen, thus minimizing the possibility of a conditioning or "priming" reaction. From our observations, 4 mg. of estrone and 1 mg. of estradiol appeared to be equivalent in hormonal activity. Within the scope of the present procedures, the lag-time of estradiol was slightly less than that of estrone; however, no significant differences were noted in the duration and degree of follicular reaction. In another series of cases treated with a variety of estrogenic preparations over a wide range of dosage, we found that the duration and degree of the vaginal response were directly proportional to the amount of hormone administered. Furthermore, the lag-time was inversely proportional to the size of the dose.¹

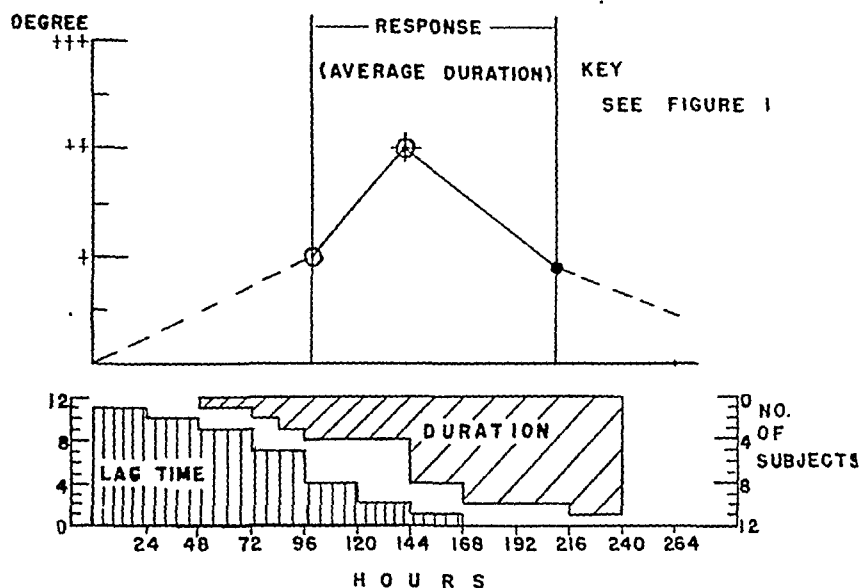


Fig. 3.—The averaged response of eleven subjects to a single injection of 0.5 mg. estradiol.

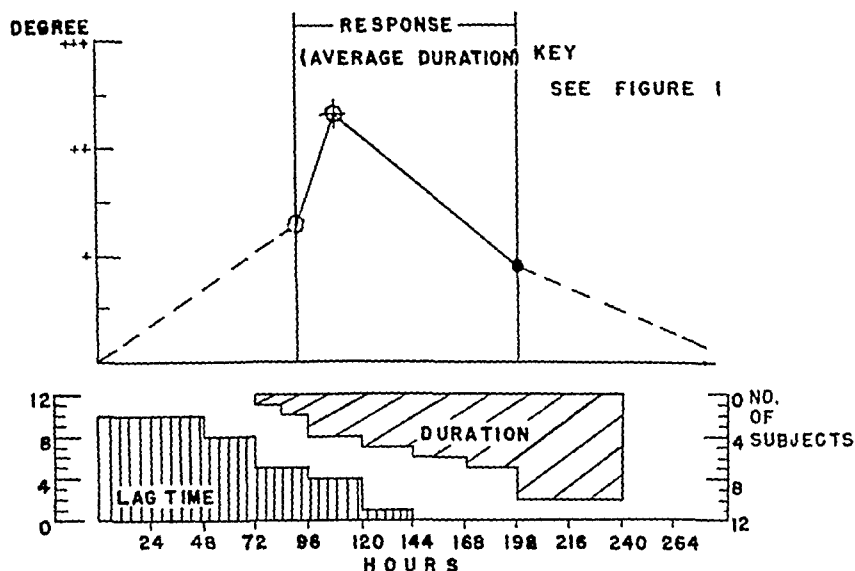


Fig. 4.—The averaged response of ten subjects to a single injection of 1 mg. estradiol.

of great importance to the practicing clinician, as he is continuously on the alert for an estrogen which will remove all symptoms of the climacterium without reactivating the uterine and vaginal mucosa. It would seem that neither estradiol nor estrone meets these requirements ideally, nor is one significantly better than the other. However, when properly administered, satisfactory relief of climacteric symptoms may be maintained by either one over long periods of time with a relatively low incidence of undesirable bleeding from the lining membrane of the uterus.

Conclusions

The vaginal mucosa of the majority of climacteric women reacts objectively to one or more injections of estrogen, not exceeding 1 mg. of estradiol or its equivalent of estrone (4 mg.) in any single dose.

The individual variations in lag-time, duration, and degree of estrogenic response are considerable, due to such factors as age, hormonal balance, and previous therapy. However, when data are averaged, it appears that the time elapsed between the injection of estradiol and a graded response was slightly shorter than the corresponding value for estrone. The duration and degree of activity are similar in all preparations tested.

Observations of daily vaginal smears lend support to the theory that repeated injections of estrogen condition or "prime" the vaginal epithelium to the further influence of the ovarian follicular hormone.

Varying degrees of symptomatic relief have been observed in a high percentage of climacteric women following one or more injections of an estrogen. The relief of subjective symptoms precedes appearance of alterations observed in the vaginal smear and can be directly correlated with them only in a very rough way.

Summary

1. Twenty-three women with climacteric symptoms have been treated successively with aqueous suspensions, containing respectively 2 mg. estrone, 4 mg. estrone, 0.5 mg. estradiol and 1 mg. estradiol. A minimum period of three weeks has been allowed to elapse between each two subcutaneous injections. A total of 80 tests has been made.

2. Control vaginal smears were taken daily for several days prior to therapy and daily thereafter for an average period of eleven days. Approximately 1,100 vaginal smears have been examined.

3. The injection of estrogen was followed by some degree of follicular stimulation of the vaginal epithelium in 69 per cent of the test subjects.

4. The average "lag-time" following the injection of (a) 2 mg. of estrone was 120 hours; (b) 4 mg. of estrone, 101 hours; (c) 0.5 mg. of estradiol, 99 hours; and (d) 1 mg. of estradiol, 91 hours.

5. Estrogenic effects on the vaginal mucosa due to the injection of (a) 2 mg. of estrone lasted 120 hours; (b) 4 mg. of estrone, 110 hours; (c) 0.5 mg. of estradiol, 110 hours; and (d) 1 mg. of estradiol, 104 hours.

Why does a patient respond to one estrogenic preparation and not to another? Patients 6a and 21a reacted objectively at both dosage levels of estradiol and at neither of estrone. Patient 14a was vigorously influenced by both injections of estrone, but only slightly by the larger amount of estradiol and not at all by the lesser. In Cases 14a and 21a, vaginal changes, capable of gradation, occurred following the third and fourth injections of the series. Patients 2a and 23a exhibited estrogenic alterations of the vaginal smear only following treatment with 1 mg. of estradiol, which, in both instances, was the final injection of their series of four each. The possibility of "priming" of the mucosa by previous therapy, although not always evident on control smears, cannot be overlooked. However, this explanation does not hold for Subject 6a, who received alternate injections of estrone and estradiol and responded only to the latter preparation. In view of the fact that a postmenopausal sexual rhythm has been demonstrated,⁴ one may postulate that, depending upon hormonal status of patient at the time, the injection of estrogen could result in either augmentation or inhibition of endogenous endocrine activity.

In four instances, a second injection of any given preparation initiated a lesser degree of activity than the first. The presence of a relatively high percentage of cornified cells and superficial cells in the vaginal secretions of some untreated castrates and postmenopausal women indicates that other endocrine structures play a part, albeit a minor one, in the maintenance of the vaginal mucosa in the absence of the ovary.

The difficulties involved in interpreting the objective changes following test doses of estrogens are paralleled by those attendant upon symptomatic analysis. For instance, in the climacteric patient psychological factors may be and usually are important. Patient 19a was a highly irritable, neurotic surgical castrate, who entered the hospital demanding frequent injections of estrogen. For a period of three weeks prior to actual hormone therapy, she was given a series of injections of sterile water, one every third day, which she alleged markedly alleviated her symptoms, but only temporarily. It is equally important not to discount the symptomatic improvement in patients such as 15a. She was a 28-year-old castrate, who, when first observed, presented a long entangled list of complaints running the gamut of the menopausal syndrome. She was successively given injections of each of the four preparations at intervals of three weeks, with dramatic improvement in all her symptoms and in her "sense of well-being." Indeed, by the end of the period of four injections she had experienced a nearly complete change in personality. Smears were taken daily throughout this period and showed *no* indication of an estrogenic stimulation of the vaginal mucosa.

From Table IV, it is clear that approximately half the subjects who obtained some degree of symptomatic relief also showed recognizable alterations in the vaginal mucosa.

As a rule, when relief was complete, the vaginal reaction was positive.

In other words, the degree of improvement and the incidence of estrogenic effects upon the vaginal secretions varied directly. These observations are

VAGINAL REMOVAL OF THE UTERUS BY MORCELLATION*

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STATISTICALLY, vaginal hysterectomy is a safer procedure than abdominal hysterectomy.^{1, 2, 3, 6} In addition, according to the testimony of the patient who has had a previous laparotomy, it is definitely a less painful experience. Simple vaginal hysterectomy can be done more quickly than abdominal removal but, technically, the vaginal approach is a bit more exacting for the surgeon. These demands on the technical skill, time, and strength of the surgeon are increased in proportion to the extent and location of the pathology to be removed. These increased demands, however, should not deter him from his efforts to acquire and constantly improve or extend these techniques in the interest of safety and comfort of his patient. Many vaginal hysterectomies are denied patients because of the increased size or fixation of the uterus. These contraindications are only relative and should be determined by the surgical skill, stamina, and judgment of the operator.

Delivery of an infant through the vagina has been proved to be a safer method of birth than any abdominal procedure. Even traumatic vaginal deliveries are attended with less shock and possibilities of peritoneal infection than are those by the abdominal route. The high resistance of the pelvic peritoneum and the lack of exposure and trauma of the other important abdominal viscera are undoubtedly essential features in this difference. We are able, in delivery of a child, to introduce the hand or instruments into the vaginal canal or uterus and deliver intact a nine- or ten-pound mass of tissue. The following morning the patient usually feels well enough to ask to sit up, or, in these days of early ambulation, even to go home. The normal vaginal tract of a woman who is not pregnant is also large and dilatable enough to allow us room for adequate exposure and removal, by morcellation, of similar masses of pathologic tissue from the pelvis.^{6, 7} The anatomy of the vagina, with its elastic walls and possibilities for incisional enlargement, make it one of the most ideal passages in the human body as an approach for removal of diseased tissue from the lower abdomen. The enlargement of the vaginal canal by birth, which eventuates in the prolapse of the uterus, bladder, and bowel, not only points the way to vaginal removal but frequently demands coincidental reconstructive repair as an important last stage in our operative procedure. Certainly, the available space, even in the virginal vagina, is many times greater than that of the nasal, aural, bronchial or urethral canals through which major surgical procedures are regularly performed. The increased safety and comfort to the patient by the morcellation

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6. The height of the estrogenic response in the vaginal mucous membrane varied widely and could not be correlated with the amount of hormone administered.

7. Certain factors involved in producing alterations in the objective response have been discussed.

8. Symptomatic relief was experienced by twenty-one of twenty-three women following injection of one or more estrogenic preparations. A cumulative action could be demonstrated as a result of repeated injections.

9. Complete or partial amelioration of climacteric symptoms cannot be directly correlated with the objective response.

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327 who required reconstructive surgery. Still further comparisons can be made by another regrouping into 219 in whom morcellation of the uterus was necessary and 421 where the corpus was removed intact.

Vaginal hysterectomy without vaginal repair	313
Vaginal hysterectomy with repair	327
	<hr/>
Total	640
 Vaginal hysterectomy requiring morcellation	 219
Vaginal hysterectomy without morcellation	421
	<hr/>
Total	640

The complications arising during operation in the entire group were few. In one patient, rather severe evidence of shock appeared during the later stages of an extensive anterior and posterior repair following the vaginal removal of the uterus. Cessation of anesthesia, starting blood transfusion and intravenous glucose solution promptly improved the condition of the patient so that the operation could be safely completed. Subsequent blood transfusions were given. The convalescence was uneventful and the patient was discharged from the hospital on the twelfth postoperative day.

A small opening was made into the urinary bladder as it was being separated from the anterior wall of a uterus which required morcellation for removal. This lesion healed by primary intention following immediate closure and drainage for eight days with an indwelling catheter. This is the only known important injury to the urinary tract in this group of 640 patients.

Carcinoma of the uterine body was encountered five times. We believe this finding should indicate routine preliminary dilatation of the cervix and curettage before vaginal hysterectomy is undertaken. This should be especially true if morcellation or opening of the uterine cavity becomes necessary during the course of the operation. Three of these carcinomas were early and the gross or preliminary examination of the uterine scrapings were thought to be benign findings. In another, cancer was suspected, due to the type and quantity of the tissue obtained by curettage. Benign hyperplasia was the diagnosis made in the laboratory from frozen section. Celloidin sections revealed definite adenocarcinoma of the endometrium. X-ray treatment followed this diagnosis. In the fifth patient, the diagnosis of carcinoma was made grossly. Three thousand mg. hours of radium were immediately given and the usual course of x-ray begun one week later. At the end of five weeks, a complete vaginal hysterectomy and salpingo-oophorectomy were done. The three early cases were done on April 12, 1939, March 26, 1944, and Oct. 4, 1946. Two of them are alive and apparently well. One of them, operated upon on March 26, 1944, re-entered the hospital and was operated upon by the general surgical service on Feb. 15, 1948, for partial bowel obstruction due to a mass of grossly malignant tissue in the pelvis. A colostomy was done but no sections were removed for confirmatory evidence. The patient in whose case the frozen section was in error was operated upon July 29, 1936. She was 63 years of age, weighed 200 pounds, and her blood pressure was systolic 200, diastolic 120. The electrocardiogram indicated an arteriosclerosis involving the coronary artery. Our recent efforts to trace her have been ineffective and we presume that she is dead. The fifth patient was operated upon April 15, 1939. She was given further x-ray in 1941 for a probable recurrence, and since that time we have been unable to trace her.

The commonest postoperative complications occurring in all groups were cystitis, delayed postoperative hemorrhage, and pelvic abscess. The complications were quite evenly divided among the various groups.

of the enlarged prostate with the resectoscope, as compared with the older suprapubic method, thus minimizing soiling and trauma of the peritoneal cavity, is a striking example of improvement in results by an approach to the pathology through a natural passage.

Most reports dealing with vaginal hysterectomy have dealt only with overall mortalities and morbidities. Few critical attempts have been made to evaluate the relative importance of the various procedures such as morcellation of an enlarged uterus, removal of the adnexa, or vaginal repair, when they have been added to the procedure of vaginal extirpation of the uterus. Much of the discussion of these reports has been concerned with size and position of the uterus which can be safely removed through the vaginal canal. The extensive changes in anatomic relationships and wide dissections necessary for the repair of uterine and pelvic floor prolapse, which is the usual indication for vaginal hysterectomy in many clinics, have never been properly evaluated as factors causing increased morbidity or mortality. We believe that repair of prolapses is, as a group, the most difficult and dangerous of any of the vaginal procedures. In such cases, injuries to the displaced bladder, ureters, and rectum are more apt to happen than when the organs are in their normal position. Bleeding is more pronounced from the dilated vessels and accurate hemostasis is more difficult. The simplest and safest hysterectomies are those performed on nulliparas.

This study of 640 patients who have been subjected to vaginal removal of the uterus and its associated procedures is an attempt to clarify some of these questions. Admittedly the group is small for statistical comparison. Furthermore, when this number is reduced by division into subgroups, the chance for error becomes even greater. We have felt that the uniformity in care might offset these errors somewhat, and that certain suggestive conclusions could be safely drawn.

These patients were all operated upon during the years from 1931 to 1947 (August) by one operator in the same hospital with only slight variations in technique. Most of them form a part of the larger group which has been recently reported from our clinic by Dr. Zeph B. Campbell.³ They represent results obtained during the period as a novitiate as well as during the more mature phase of operative experience. The most important variables which have occurred in this series have been a gradual improvement in the preoperative preparation of the patient and perfection of operative technique, more frequent employment of blood or plasma, and the addition of the antibiotics. Sodium Pentothal as a means of induction has been the only important change in anesthesia.

For comparison, this series of patients has been divided into six groups:

1. Simple vaginal hysterectomy	129
2. Vaginal hysterectomy with repair	249
3. Vaginal hysterectomy by morcellation	125
4. Vaginal hysterectomy by morcellation with repair	78
5. Vaginal hysterectomy with removal of one or both adnexa	43
6. Vaginal hysterectomy by morcellation and removal of one or both adnexa	16
Total	640

The various groups can be regrouped conveniently into two main divisions of about equal numbers, 313 patients in whom no vaginal repair was done and

cent. Since prolonged bleeding with its consequent anemia has been described as an important factor in thrombophlebitis and pulmonary embolism, it is noteworthy that no patient died as a result of embolism, although, in two patients, x-ray evidence indicated that small pulmonary embolic infarctions had occurred. Pulmonary embolism stands high among the causes of death in the reported cases following abdominal hysterectomy.

Tabulated according to the usual morbidity standards with which we do not agree,³ one hundred sixty-nine patients, or 26.4 per cent, were morbid. We agree with Jones and his co-workers⁸ that morbidity figures would mean much more if they included only those conditions which complicate or delay the normal course of convalescence or are followed by symptom-producing sequelae. There were 610 days of morbidity in these 169 patients. The average morbid days were greater in those patients in whom vaginal repair was added to straight vaginal hysterectomy. This fact may be accounted for partially by the greater number of extensive prolapse cases that are included in this group. Morbidity was less in those patients subjected to vaginal morcellation of the uterus but proportionately more than in the remaining operative procedures. These figures for morbidity are reflected in the average days of hospital stay. However, a review of those patients operated upon since the advent of early ambulation indicate that these proportions may be changed in future studies. It is quite certain that the average hospital stay of 12.9 days will be appreciably and safely decreased.

The only death that occurred in this series followed vaginal hysterectomy and repair in a multipara with rheumatic heart disease. Death resulted from an unrecognized small bowel obstruction caused by an adherent loop of ileum to the vault of the vagina. The clinical course was confused by the coincident cardiac symptoms. However, in retrospect, a review of this patient's clinical course leaves little or no excuse for failure in diagnosis of the obstruction and it should have been an easily prevented death. The mortality rate for this series of 640 cases then was 0.16 per cent, which is lower than the 0.32 per cent previously reported³ for the larger group of which these patients are a part. Since the pathology in about one-third of these patients was as extensive as that used for the usual indications for abdominal removal, it would seem that a comparison of mortality rates with a like number of abdominal hysterectomies would be fair and suggestive. Compared with the rates reported from representative large clinics I think the answer is obvious; 2.4 per cent against 0.32 per cent to 0.16 per cent.

As one would expect, the greatest number (452), or 70 per cent of these uteri were removed from patients 40 years old or older. Many of those younger than 40 years, were operated upon for conditions other than vaginal hemorrhage such as painful adenomyomas, intrauterine fibroids, cervical strictures, recurrent polyps, or as a method of sterilization and an integral part of pelvic floor repair. Three of them were operated upon for prolonged intractable bloody discharge following previous intrauterine radium which had been given elsewhere for uterine bleeding. We believe that this entire group of women was treated more conservatively and probably as safely, by vaginal hysterectomy than they would have been by the widespread killing action of irradiation.

In our opinion, castration irradiation for benign disease is one of the most destructive of gynecologic operations. All function is destroyed, leaving useless organs in which distressing sequelae or cancer may later develop.

In summarizing the experience gained in operating upon the 640 patients reported above, we believe that vaginal removal of the uterus by morcellation is as safe as, and certainly more comfortable for the patient than, other forms of hysterectomy. Judgment gained by experience in evaluating the accessibility of the important blood vessels, anterior and posterior cul-de-sacs, and the com-

Cystitis occurred almost twice as frequently, however, in those patients subjected to morcellation of the uterus as in those in whom simple vaginal hysterectomy was performed. This fact, coupled with the increased frequency of cystitis in vaginal hysterectomy without incision of the vaginal walls, suggests that it may be due to the mechanical manipulation of the tissue in the confined space of the vagina. We have limited the diagnosis of cystitis to those patients in whom elevated temperature or urinary findings delayed the patients' normal recovery, or persisted until the postoperative office visit. Transient temperature elevations, urinary dysfunctions, and cellular reactions in the urine, we believe, are as much a normal reaction to the necessary operative trauma in vaginal surgery as is the postoperative leucocyte-laden serous vaginal discharge that occurs in almost every patient. We do not believe that they should be used as an argument against vaginal hysterectomy any longer. Several of the persistent cases of cystitis were found to have bladder polyps, diverticula, or a coincidental urethritis and vaginitis. Subsequent treatment of these conditions improved or cured the urinary symptoms.

Delayed postoperative hemorrhage occurred more than twice as frequently in those patients requiring vaginal plastics. In four of the total of ten patients, the bleeding arose in the anterior or posterior vaginal incision, while, in the remainder, a small vessel in the corner of the vaginal cuff seemed to be the origin of the bleeding. In most instances, the edges of the incision were widely separated, suggesting pressure from a previous hematoma or infection. Infection seems to be the more probable since pelvic abscess occurred four times as often following repair as in those patients who were subjected to vaginal hysterectomy alone. In previous years, attempts were made to control postoperative hemorrhage by packing the vagina tightly with cotton tampons. However, this occasionally placed undue tension on the vaginal incisions with partial separation of the repair. More accurate hemostasis is now obtained by prompt resuture with a minimum of trauma to the previously repaired surrounding structures. In one instance, however, during resuture for bleeding which had occurred for the second time in the same patient, a rectovaginal fistula was produced. This fistula closed after fulguration of the fistulous tract and the patient has had no further difficulty. Accurate hemostasis following morcellation of the uterus is possible because postoperative bleeding occurred in only two patients on whom this procedure was carried out. In two instances, the postoperative bleeding occurred within twelve hours following operation, indicating that primary suture was inadequate. The remainder occurred from five to twenty-one days postoperatively. The loss of blood was severe enough in three patients to require blood transfusion, although blood was given to several others as a prophylactic measure.

Postoperative respiratory difficulties were about equally divided among the various groups. They have been less frequent than in a comparable group of laparotomies. This might be expected on account of freer ambulation and decrease in splinting of the abdominal muscles by pain or abdominal supports following laparotomy. This fact may also help to explain the low incidence of thrombophlebitis. One such instance occurred following vaginal hysterectomy with repair, and the other followed morcellation of the uterus. As has been mentioned, we believe that preoperative eradication of foci of infection and blood transfusion are the more important factors in preventing this serious complication.

A total of one hundred fifty transfusions were given, 94 before operation and 56 following operation. One patient entered the hospital for vaginal bleeding with a hemoglobin reading of 6.5 Gm. She received five preoperative 500-c.c. blood transfusions, and two after operation. Twenty-five per cent of the entire group of patients entered the hospital with their hemoglobin below 70 per

cases. This complication I know no way to prevent, unless intramenstrual bleeding may give us a possible clue. The average hospital stay in this series was fourteen days. During the last year, this has been reduced to twelve and one-half days. There was one death in our series. This patient died of cardiac decompensation.

DR. RALPH A. REIS.—We have heard the painstaking review of a series of cases with most excellent results. Once again I think we should be impressed with the value of vaginal hysterectomy. Vaginal hysterectomy is well established. It is nothing new. At Michael Reese Hospital, vaginal hysterectomy was done long before total abdominal hysterectomy was done, just as it was done elsewhere. At the present time at Michael Reese Hospital, our group is doing a little better than 60 per cent of all hysterectomies by the vaginal route and 40 per cent by the abdominal route. Likewise morcellation is nothing new. Pean employed morcellation in 1873. If you read Doyen, you will find that, in 1895, he described fourteen or fifteen methods of morcellation. I confess that we at Michael Reese Hospital have, on occasion, done morcellation as is done at St. Luke's Hospital and at Presbyterian. I wonder why the proponents of vaginal hysterectomy would need to defend the procedure. Nobody questions its value. No one should bring up the point which Dr. Edwards mentioned, that we must know how to do hysterectomy before we discuss it. I would prefer to go on the assumption that those of us here now are equally competent to do vaginal as well as abdominal hysterectomy. I think each method has its distinct and definite place. We believe that hysterectomy should be done by the vaginal route except when there is either definite malignancy or suspicion of it, when there has been previous pelvic surgery, when there is adnexal disease with fixation or fixation plus an adnexal mass that is large. It should be done vaginally except when tumors are intraligamentous or adherent. Finally, it should be done vaginally unless the uterine mass in toto is larger than that of a twelve to fourteen weeks' pregnancy.

I should like to request of Dr. Allen, as I have previously of Dr. Campbell, not to compare the present-day statistics and their excellent results in vaginal hysterectomy with the older statistics for abdominal hysterectomy. I question whether any major institution in this area shows a mortality rate of 2.4 per cent, i.e. one death for every forty abdominal hysterectomies.

Recent statistics only as far back as the beginning of 1946, disclose a first report of Tyrone from the Ochsner Clinic. He lost one patient in 507 by the abdominal route, 0.2 per cent.

The next report is Feeney of Dublin who lost one in 388, that is 0.25 per cent.

The next is Siddall from Harper Hospital in Detroit. He lost one in 150, that is 0.76 per cent.

Finally from this Society, Danforth, Sr., at Evanston Hospital lost one in 250 and two in 500 reported, which is 0.4 per cent.

Those figures are a long way from the 2.4 per cent we heard tonight that is being used in comparison with vaginal hysterectomy.

Now let us consider the recent statistics for the vaginal hysterectomies. Campbell who has a large series had one in 310, which was 0.32 per cent.

Falk, in New York, reported one in 500, 0.2 per cent.

Allen who reports the best results, has one in 640, which is 0.16 per cent.

I concede that there is a slight difference in the mortality between abdominal and vaginal hysterectomy. But there is not anything like the marked difference that the essayist would lead us to believe. Dr. Leventhal is analyzing comparable hysterectomies at Michael Reese Hospital at the present time. In several hundred hysterectomies performed vaginally and abdominally for the same type of pathology, there is no difference in morbidity and mortality. Actually, in the last several hundred, there has been no death in either series. I still maintain that hysterectomy by either route has relatively precise indications. Large fibroids should be removed by the abdominal route.

DR. A. F. LASH.—I heartily agree with Dr. Allen regarding vaginal hysterectomy. I should like to show you a safer method of doing morcellation without opening the uterine

ponent parts of the uterine tumor is more important than size alone. The post-operative morbidity, mortality, and complications, with the exception of cystitis, were less frequent in this group of patients than in those who required coincidental vaginal repair.

Discussion

DR. EUGENE A. EDWARDS.—Certainly no gynecologic staff is more qualified to report their experience with vaginal hysterectomy than is the group from Presbyterian Hospital.

I believe Dr. Allen's conclusion that vaginal hysterectomy with morcellation is a safe operative procedure is justified, as is evidenced by the good results he presents. However, we must remember that the operator of these cases is thoroughly trained in vaginal surgery, and years of continuous doing has greatly added to his experience. I believe that vaginal hysterectomy with morcellation is a safe procedure when performed by one who has had such training.

Our experience is not as extensive as is reported in this series. We have performed 42 morcellation operations in 570 operations, with complete success in all of them.

I believe the simplest vaginal operation is the removal of a bleeding uterus from a nullipara. The next easiest vaginal hysterectomy is the removal of the fibroid, freely movable uterus approximately the size of a 3 or 3½ months' pregnancy by morcellation. The repair of the anterior and posterior vaginal walls in association with vaginal hysterectomy complicates the operation because of the much more extensive bleeding. Previous vaginal surgery, where a repair has been performed or where radium has been used, also greatly complicates the vaginal removal of the uterus.

The removal of the fibroid uterus that extends to the umbilicus or above is probably best accomplished through an abdominal incision. However, an attempt should be made to remove this large a tumor by vagina, when associated with cystocele. I know of no way to cure a cystocele unless it is repaired vaginally. The removal of such a tumor may not seem possible; however, if an attempt is made, it is surprising how many times its removal is accomplished. If, on the contrary, it is impossible to remove the tumor, the uterine arteries are tied off, the cystocele is dissected out and the hernia is repaired by suture to the uterosacral ligaments. Then the abdomen is opened and very easily the ovarian arteries are ligated and the uterus removed.

There are certain indications and contraindications to vaginal removal of the uterus:

1. The operator must be experienced in vaginal surgery.
2. A correct diagnosis is most important.
3. Intraligamentous fibroids and fibroids under the urinary bladder are best removed abdominally.
4. Abdominal pain usually contraindicates vaginal hysterectomy.
5. Intramenstrual bleeding usually complicates vaginal surgery.
6. Endometriosis may or may not complicate vaginal hysterectomy.
7. Ovarian tumors and carcinoma of the endometrium, except in the rare cases, contraindicate vaginal surgery.

Cystitis is also the most frequent complication in our series. However, in our experience, the repair of cystocele is the main factor in its etiology. In the 49 cases of cystitis, 41 had cystocele repair. We opened the urinary bladder five times, but each time it was detected, sutured primarily, and on no occasion did it influence the postoperative clinical course. We injured the ureter in two cases.

Postoperative bleeding has occurred in our series nine times, once on the sixth postoperative day, the others from the ninth to the eighteenth postoperative days. Resuture was necessary five times. Phlebitis occurred only once in our series. This was localized to a superficial vein and was of no serious consequence. There were no emboli in our series.

Three times carcinoma of the endometrium was encountered. We now try to prevent this serious problem by curetting all cases. Sarcomatous degeneration was encountered in two

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cavity. Occasionally we find in older women a pyometra or carcinoma which had not been suspected. After the tying of the uterine arteries, the uterus is removed by shelling out the myometrium around the uterine cavity, followed by turning out the remaining myometrial shell and usual removal. In carcinoma, there is danger of spillage and that is one of the objections to morcellation. After the uterine cavity is removed, the uterus can be further reduced in size by bisection. Further, I believe that in all women past 45, when the uterus comes out, the tubes and ovaries should come out, too. We do it quickly and regularly when we do an abdominal hysterectomy and there is no reason why we should not do it vaginally.

The next observation made regarding vaginal hysterectomy is that there are fewer ovarian cysts following vaginal hysterectomy than following abdominal hysterectomy.

Regarding bladder disturbances, I think in many instances we have a paracystitis rather than a true cystitis.

In spite of the fact that we have broad indications for vaginal hysterectomy, I do not believe in surgical acrobatics. There are many instances in which a woman has bowel symptoms and the abdominal approach is necessary. Every once in a while, about once in two years, we meet a carcinoma of the rectosigmoid where neither the symptoms nor the clinical findings pointed to it. There have been instances where the x-ray did not demonstrate carcinoma and yet there was a carcinoma in the rectosigmoid on opening the abdomen. It is, therefore, evident that our enthusiasm must be tempered by good judgment.

DR. ALLEN (Closing).—I am glad Dr. Edwards agrees with the safety of morcellation because so many times, as I said in the opening of this paper and in the discussion at the clinical meeting, the younger men say it is a stunt. I do not believe it is a stunt. We are firmly convinced of its value. We are not the ones who are on the defensive. I do not think we have to be on the defensive in a discussion of vaginal hysterectomy, especially from the standpoint of rapidity, increased safety to the patient, and comfort to the patient if nothing else.

I quite agree with Dr. Edwards about the location of the tumor. Tumors that are under the bladder, even if small, or immediately over the area of important blood vessels as they come into the side wall of the uterus are a contraindication often to either vaginal removal or morcellation. If one cannot reach those vessels rather rapidly then we agree that the tumor should be removed abdominally.

As far as statistics go, I would like to repeat a few that were reported in Dr. Campbell's paper, in which we took figures from a comparable time not only in operative technique but the various adjuvants of safe surgery, blood plasma, antibiotics, and increased knowledge of surgical technique, and in which we derived a mortality rate of 2.5 per cent. These were taken from clinics here and other notable clinics. Smith reported 1,837 cases with six deaths; Miller, 629 cases with 12 deaths; King, 537 cases with 5 deaths; Williams, 1,870 cases with 52 deaths; Mengert collected 1,925 cases with 38 deaths; Bryan, 842 cases; McDonald, 2 cases; Masson at the Mayo Clinic, 2,184 cases with 21 deaths, Dannreuther, 425 cases with 9 deaths. We reported at that time a comparable series of 898 cases with 10 deaths. This report I made tonight goes back to when I began to operate. If I were to take off the earlier cases there would have been no mortality. I do not think it is a fair thing to compare this last year of anybody's series with a period of 16 years back. I think you have to take a long period of observations to make it fair. When you do that you will find that vaginal hysterectomy carries a lower mortality and certainly more comfort to the patient.

I am interested in Dr. Lash's description of morcellation, particularly in cases of carcinoma. I tried to bring out by reporting these five cases that we encountered the risk in morcellation with carcinoma. We have been lucky enough in having no sarcomas either in this group or the last one. One of these patients I did know had a carcinoma but I do not think vaginal hysterectomy or morcellation is the treatment for carcinoma. I tried to find out in how many cases we started to do vaginal hysterectomy not suspecting, or only slightly suspecting, that it was a carcinoma, then introducing radium, and later operating on the patient by the abdominal route. I would like to know how many cases are operated upon by abdominal hysterectomy without previous dilatation and curettage and carcinoma of the body of the uterus is not found until the pathologic sections come back from the laboratory. I believe there are a considerable number.

Results

In an analysis of this type, the following procedure was followed. The first day of menstruation was designated as day zero (0) and each day preceding the onset of menstruation as -1, -2, etc.; in that way, since the ovulation—menstruation interval is relatively constant, any deviation from this would be brought out.

Fig. 1.—Using the records of H. K. and E. K., the intermenstrual interval is shown. The consistency of the interval can be noted. During the first year, perhaps they are not quite as consistent as those during the second and third years, but the difference does not seem to be appreciable.

Fig. 2.—Using the records of H. K., a frequency distribution curve was made comparing waking and bedtime temperatures for a period of three years. It demonstrates the frequency with which temperatures of 97° F. to 98° F. and 98° F. to 99° F. occur. Although the waking temperatures are somewhat more consistent, both show the characteristic changes.

Fig. 3.—In each subject, the first three years after the menarche was divided into approximately yearly intervals. The waking temperatures reveal a pattern during the first year which is considerably different from the second and third years, the latter two showing a striking similarity to each other. This is true in both subjects. During the first year, there is no sharp break in the temperature curve at the approximate time of ovulation. In the second and third years, there is a sharp break in the temperature curve at the expected time of ovulation. The break in temperature is very consistent in each of the subjects. The pattern is established after 12 months in H. K. and 18 months in E. K. The break occurred in H. K. on day -15, while in E. K. on day -10. The first year's records in both subjects show a gradual rise beginning at the estimated time of ovulation, which eventually approaches the level of the second and third years, but instead of the majority of the rise taking place over a period of 48 hours, as is usual in the adult, it takes a period of seven to eight days. This is constant in both subjects studied and the records of the individual months bring this out even more clearly. The curve is not one of averaging the typical curve of ovulation with the classical anovulatory curve, but is typical in itself, namely, a gradual rise in temperature over a period of a week starting at the estimated time of ovulation.

Fig. 4.—To bring this out in graphic form, the following analysis was made. In H. K. the average temperature of days -21 to -14 was compared to days -14 to -7. This was done each month for a period of three years to demonstrate that during the first nine recorded periods the average temperature before and after the expected time of ovulation was approximately the same. The pattern changed abruptly about one year after the menarche. When days -21 to -14 were compared to days -7 to -1, the full nature of the curve is brought out, namely, the similarity of the pre-menstrual week in all three years. This type of analysis also brings out the occurrence of the classical anovulatory cycles. This is now being studied to try to determine a seasonal frequency, if any.

Fig. 5.—Another attempt at the graphic presentation of the genesis of the typical ovulation curve was tried but with only a moderate degree of success. Using the records of H. K., each four-month interval was treated as a unit, and the charts shown are the frequency, in percentage, with which temperatures of 97° F. to 98° F. (white) and 98° F. to 99° F. (black) occur and the day in the cycle that they appear. It is obvious from Fig. 3 that, in this subject, a progesterone effect is probably associated with a temperature over 98° F. It can be noted that during the first four recorded periods there is a scarcity of temperatures over 98° F., and when they do occur the majority are grouped during the eight days preceding the onset of menstruation. When the next four months are treated in the same way, we find a much higher percentage of temperatures over 98° F. and the majority occur during the ten days preceding menstruation. During the next four-month interval, the majority occur during the thirteen days preceding menstruation. By this time, the adult pattern is established and the following two years are remarkably similar.

THE RELATIONSHIP OF ADOLESCENT MENSTRUATION TO BODY TEMPERATURE AND STERILITY*

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THE relative infertility of women for a variable period of time after the onset of menstruation has been recorded in the literature for centuries. Most of the early reports were made by ethnologists rather than the medical profession, but the earliest recorded reference to this subject was made by the Hindu physician Susruta in 500 B.C. He stated, "If a man under 25 years deposit his germ in a woman younger than 16 years, it will most likely die in the womb . . . even if it is born alive it will die soon, or he will be weakly as long as he lives." In more recent times medical observers have noted that although sexual intercourse is promiscuous among the natives of South Australia, Melanesia, New Hebrides, the Luzon section of the Philippines, and parts of India, pregnancy as a rule does not occur until several years after the menarche. There is no known use of contraceptives in these particular groups and the "abortive herbs" which are used by some have been investigated and found to be totally ineffective. In many of these groups there is no understanding of the relationship of intercourse to conception. In recent years a great deal of experimentation has been carried out on animals to determine the nature of this sterile period. The association of nidation and the elaboration of progesterone has been demonstrated in lower animals. In monkeys the early periods were found to be extremely irregular, and thought to be anovulatory. Hartman feels that each month the ovary produces larger and larger follicles until such time as they no longer degenerate, but go on to ovulation. He also found a lack of luteinization during the early months of menstruation and when pregnancy did result there was a high incidence of abortions. In the chimpanzee the sterile period was found to be about one year after the menarche even in those females which were caged with a male before the onset of menstruation.

Procedure

The subjects used in the present study were the daughters of a university professor. Both girls were asked to take their temperatures before going to bed and again before getting out of bed in the morning (5 minute oral temperatures were used). Both subjects started recording their temperatures shortly after the menarche. In one (H. K.), it was started after her second menstrual period, at the age of 12 years 6 months, and has been continued to the present time—a period of 6 years. In the other (E. K.), the records were started after seven periods, at the age of 12 years 2 months, and are still being continued at the present time—a period of four years. The temperatures, as indicated above, have been taken twice daily during this entire period, except for brief intervals of illness. This is a study of the first three years of temperatures correlated with the menstrual flow.

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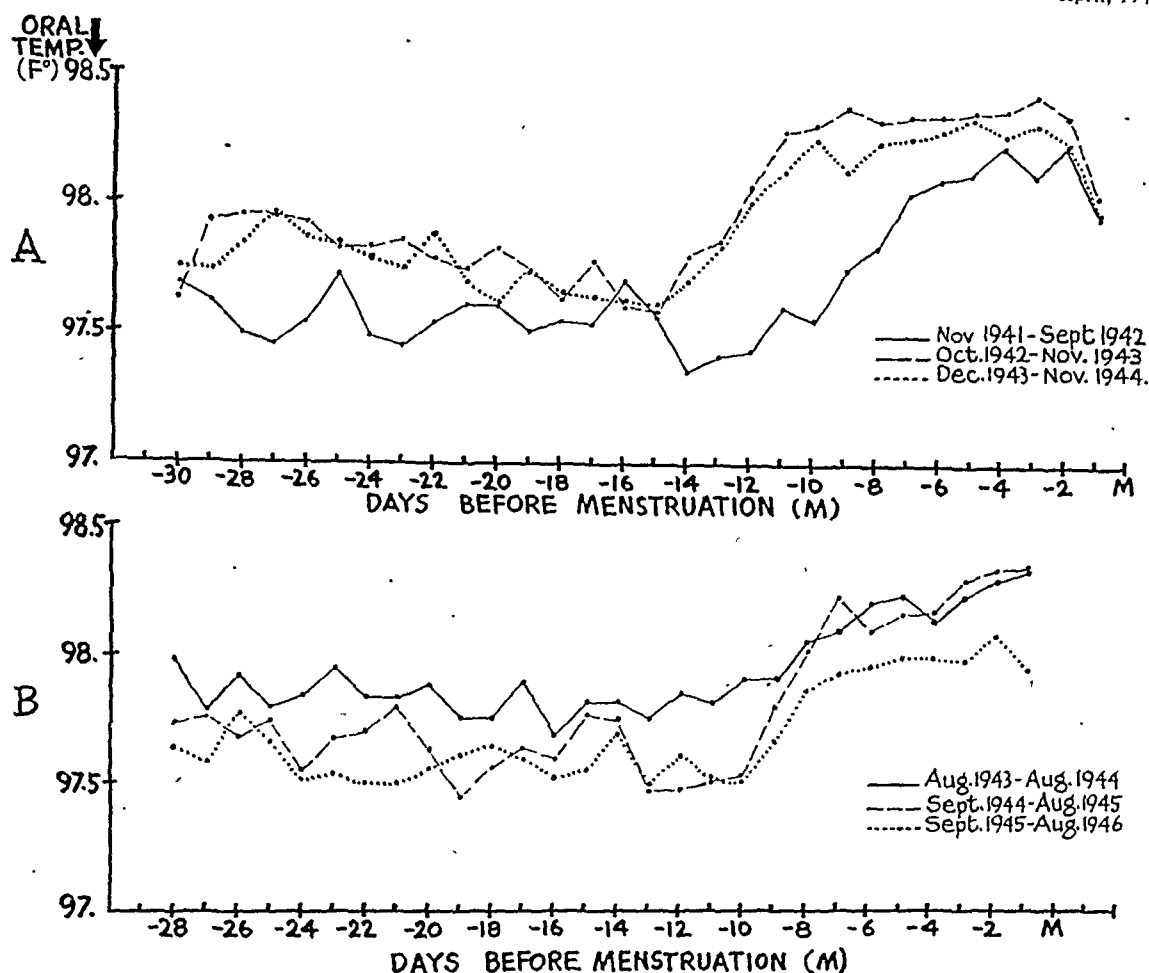


Fig. 3.—Mean A.M. temperature. (A) Subject: H. K. (B) Subject: E. K.

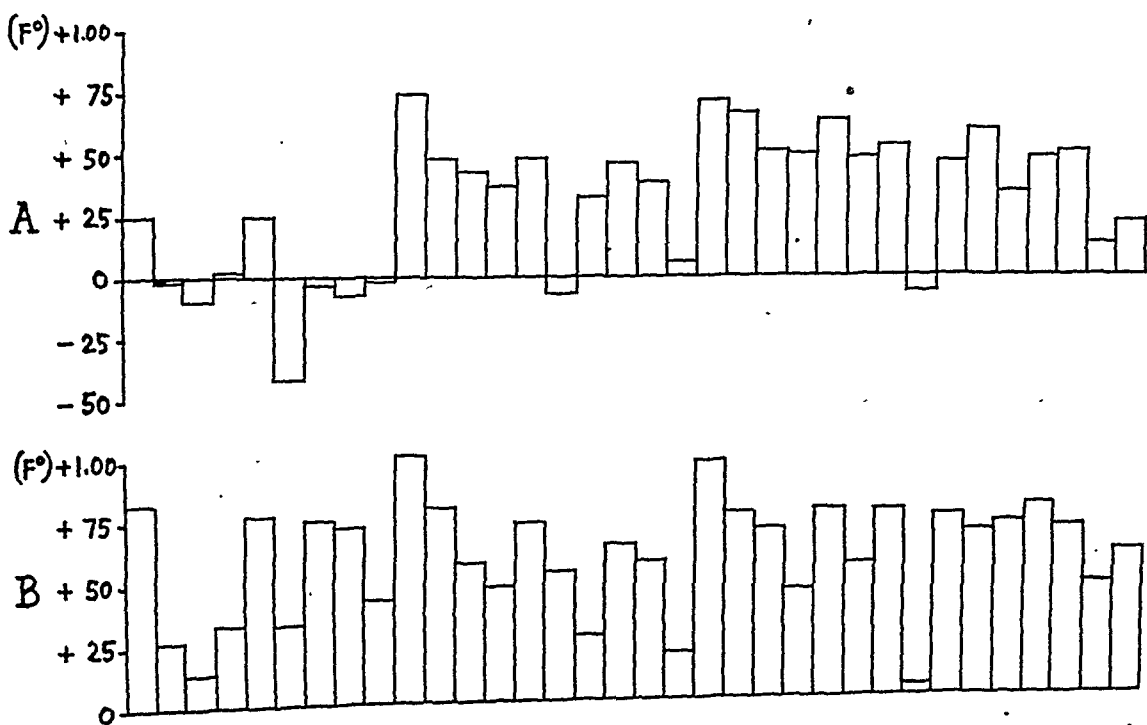


Fig. 4.—A. Average difference (F°) between days -21 to -14, and -14 to -7. B. Average difference (F°) between days -21 to -14, and -7 to -1. Subject: H. K.

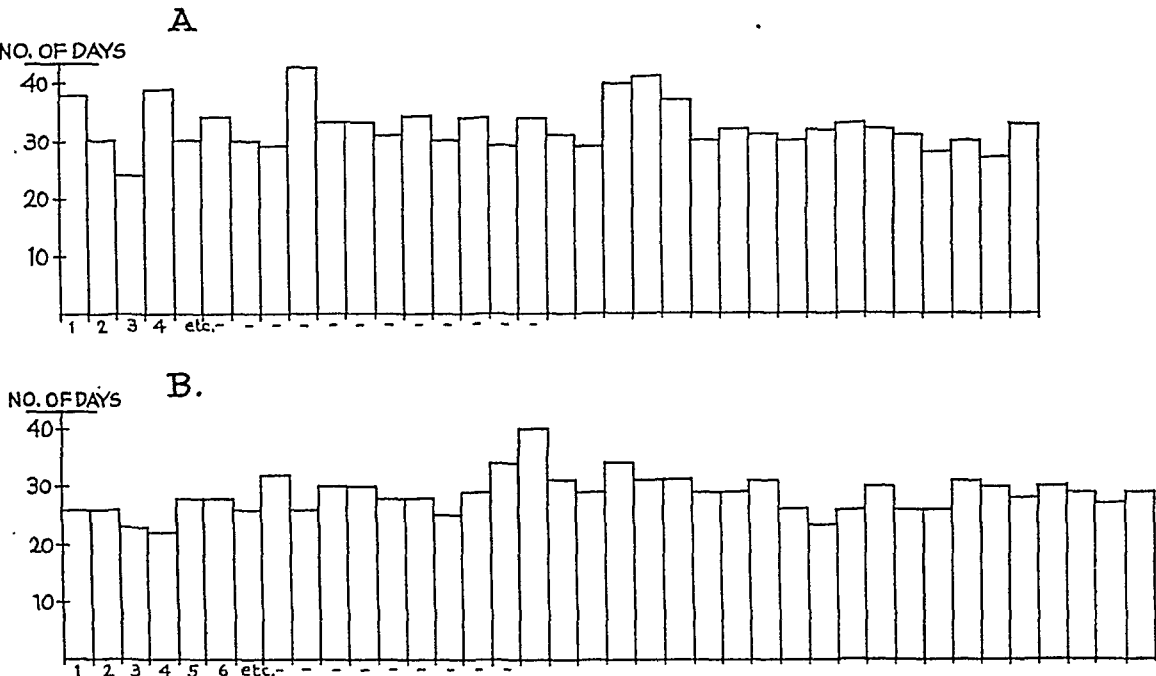


Fig. 1.—Intermenstrual interval. (A) Subject: H. K. (B) Subject: E. K.

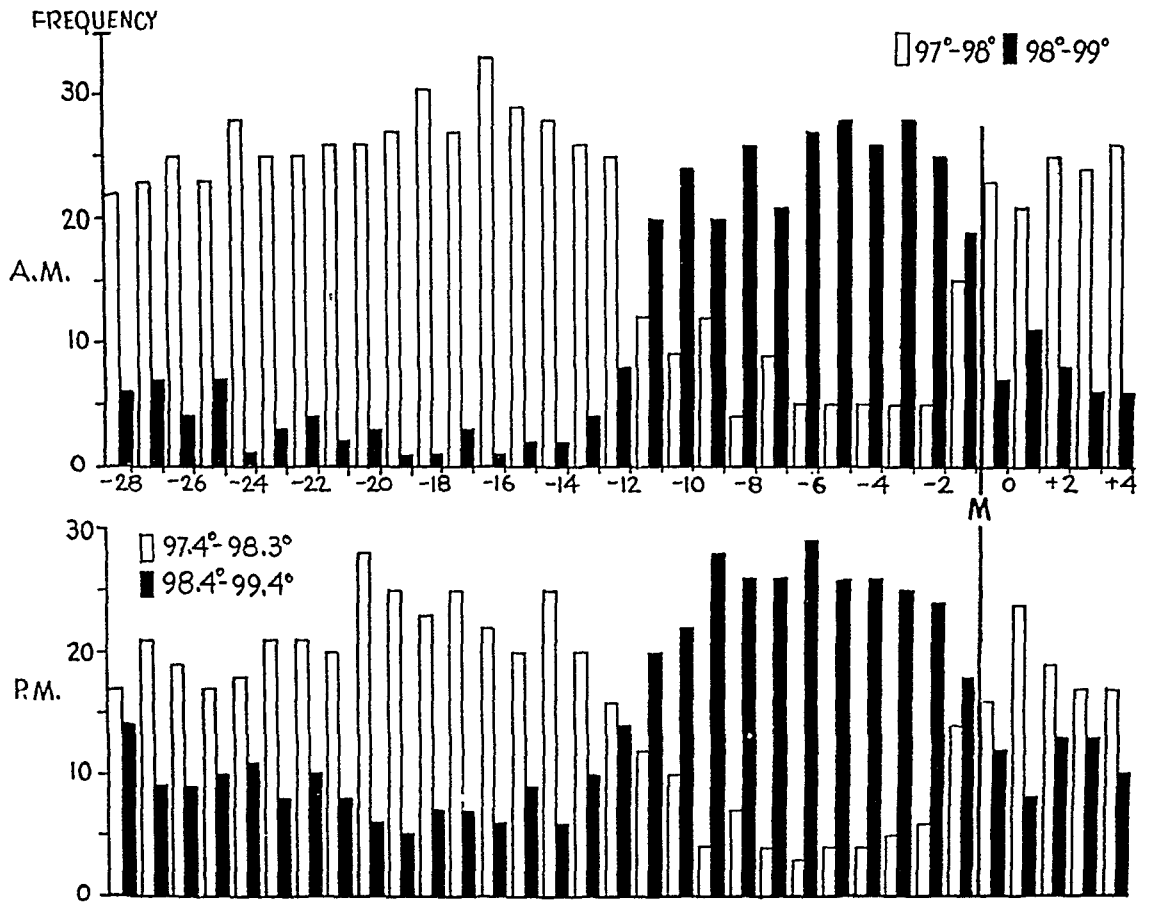


Fig. 2.—Days of the menstrual period. Subject: H. K. November, 1941, to November, 1944.

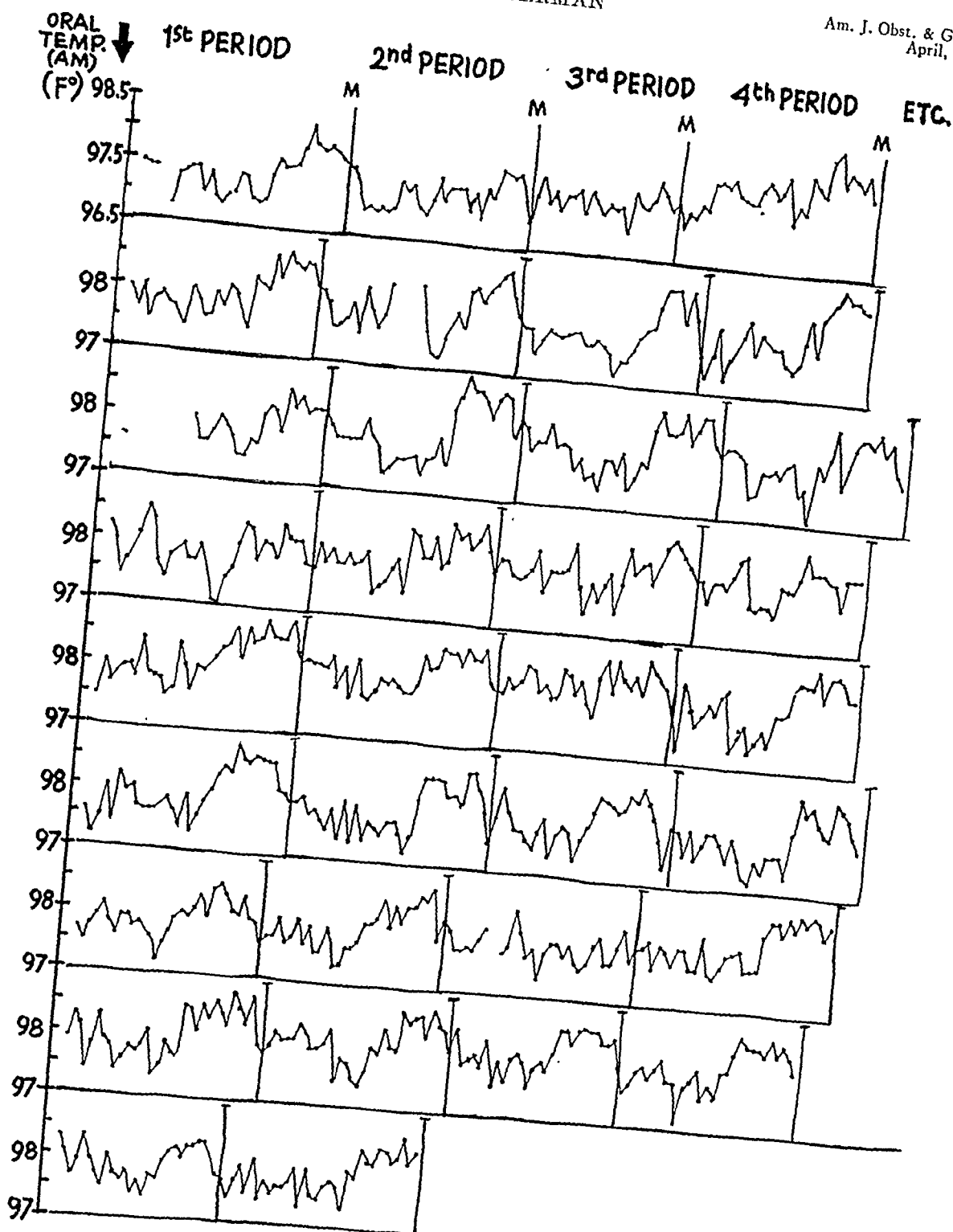


Fig. 6.—Subject: H. K. November, 1941, to November, 1941. Menstruation first day (M)
34 menstrual periods.

Fig. 6.—Using the records of H. K. and treating each menstrual period as a unit, a running chart for a period of three years is portrayed. This demonstrates graphically the change in the character of the temperature curve as one proceeds from the earliest menstrual periods to the more mature pattern. One can see that during the first nine months the temperature curve is not the typical ovulation curve. The second and third recorded periods are the classical anovulatory curves, but as one proceeds from here, they are of a

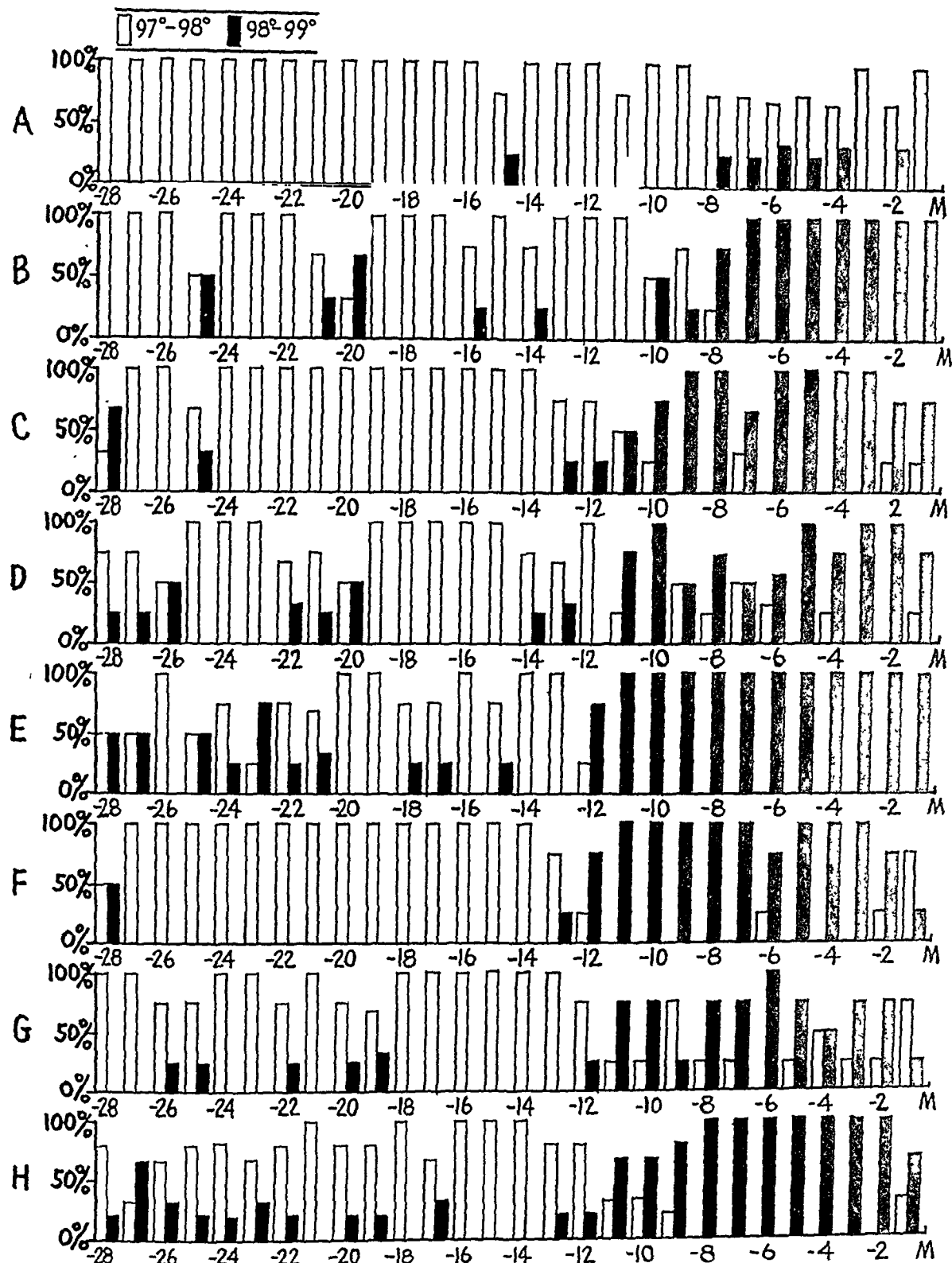


Fig. 5.—Frequency distribution. Subject H. K. November, 1941, to November, 1944.

- A. First four periods
- B. Second four periods
- C. Third four periods
- D. Fourth four periods
- E. Fifth four periods
- F. Sixth four periods
- G. Seventh four periods
- H. Last six periods.

years studied. If the accepted explanation is correct, namely, that the temperature rise is due to the action of progesterone, closely associated with ovulation, it follows that the premenstrual woman either ovulates and forms a poorly functioning corpus luteum, or luteinization of the theca and granulosa cells follows the degeneration of the formed follicle. Regardless of which explanation is correct, the functional result is sterility.

Browne and Venning demonstrated in their studies on corpus luteum function that if chorionic gonadotropin is given in daily doses of 1,000 international units in the early part of the luteal phase, there is an increase in estrogenic excretion, the pregnandiol excretion is prolonged and the endometrial biopsies show histologic changes similar to early pregnancy.

Abarbanel, in correlating several hundred endometrial biopsies with basal body temperature curves, reveals that on the whole the classically defined diphasic basal body temperature is associated with ovulation as witnessed by conception and a fully developed secretory endometrium. On the other hand, a study of various aberrations revealed a secretory endometrium of the so-called mixed type or immature progestation phase (days 19 to 22 of a 28-day cycle) when taken on the first day of menses. In these instances, the basal body temperatures were either irregular or flat.

The temperature curve of the pubescent is rather characteristic and as consistent as the ovulatory or classical anovulatory curve. This type of curve is one frequently seen in the sterile adult. I should like to designate this as the intermediate temperature curve. The sterile adult with this type of curve may very well be one whose ovaries are still functioning in the adolescent manner. Much more work will have to be done to test the validity of the last remark. If the pubescent temperature curve observed in the adult indicates luteinization of the developed follicle without ovulation, then there appears to be no rational therapeutic approach as yet. However, if this curve represents ovulation with an associated defective corpus luteum function then therapy might be directed toward stimulation of corpus luteum function or the substitution of corpus luteum hormones.

Summary and Conclusion

The use of evening oral temperatures, if properly taken, can be used in the study of sterility. This, of course, could be combined with waking temperatures during the expected time of ovulation.

I believe the results of this study give a physiologic basis for the old observations of relative infertility in the female for a period of time after the onset of the menarche. As to whether body maturity also plays a role to extend this time interval is yet to be determined.

For a period of twelve to eighteen months after the menarche in the subjects studied, a characteristic temperature curve is evident. This is different from the mature type, as well as the classical anovulatory type. I should like to designate this steplike curve as the pubescent temperature curve. It has been suggested that when this type of curve is found in the sterile adult, corrective measures may be used, if the underlying cause is an immature attempt at corpus luteum function rather than lack of ovulation.

steplike nature. The periods of elevated temperatures increase and the break becomes sharper. This is brought out more clearly when one compares the early recorded temperatures to those taken during the second and third year. During the latter period, except for an occasional anovulatory curve, they are of the mature pattern.

Discussion

The postmenarchial stages in a woman's life may be divided into four periods. The period of puberty, the period of nubility, the period of maturity, and the period of senility. The period of nubility is that interval between puberty and maturity when the female is capable of procreation without appreciable danger to herself or her offspring. During this period, not only must ovulation be present, but the elaboration of progesterone must occur in sufficient amounts and early enough to insure nidation. The interval between puberty and nubility can be referred to as the adolescent sterility period.

As to the similarity of waking and bedtime temperatures, one may find it much more convenient for the patient to take the bedtime temperature. Although the bedtime temperature is not quite as consistent as the waking temperature, with proper understanding on the part of the patient it can be used effectively in the study of sterility. To avoid hot or cold drinks just before taking one's temperature is not a chore and if bedtime is variable the temperature could be taken at a definite hour each night. I feel that, in the study of sterility, during the week before the estimated time of ovulation, both waking and bedtime temperatures should be taken, for in that way an evening shift in temperature could be twelve hours closer to the time of ovulation.

Rectal, vaginal, and oral temperatures have been used in studies of this sort, and I believe it has been demonstrated conclusively that when two types were taken simultaneously in the same subject, the results were identical. Dr. Kleitman, a recognized authority on the role of body temperature in physiological processes, has advocated the use of oral temperatures in these studies for a long time. Nieburgs demonstrated the identical nature of oral and vaginal temperatures in a sterility study. He also showed that the use of estrogens during the first half of the cycle in girls who had irregular infrequent periods tended to bring about the characteristic diphasic temperature curve.

The intermenstrual interval shows a remarkable degree of consistency. The interval between the first and second period not shown on Fig. 1 being the exception, for in both subjects it was appreciably longer than any of the subsequent periods. The consistency is quite in contrast to the results obtained by Hartman using monkeys.

The thermogenic effect of progesterone has been adequately demonstrated by many investigators. Barton and Weisner used progesterone in oil (5 to 15 mg.) daily, which caused a slight but persistent rise in waking temperature. When progesterone crystals were used, 3.5 mg. per c.c. (2×10^5 crystals), the waking temperature was elevated within twenty-four hours and a distinct diphasic curve was obtained by three injections. This curve resembled the usual curve associated with ovulation.

This material demonstrates that the temperature curve for approximately 12 to 18 months after the menarche is different from that of the subsequent

In general, it can be said that the estrogenic phase of the normal cycle is associated with a low level of the temperature and the luteal phase with an elevated level. The rise in the temperature about the middle of the average 27- to 31-day cycle occurs coincidentally with ovulation. The exact time of ovulation is still debatable; however, we have recently provided some evidence that it may often occur after the low level has been reached prior to the ovulatory rise, and as the rise is taking place. We have recently reported a group of women who conceived during the period when they were following ovarian activity by basal temperatures and, in at least one of every three, the fruitful coitus occurred simultaneously with the ovulatory rise. Gruelich removed corpora lutea from women during the period of transition from the estrogenic to the luteal phase in the temperature curve and found ovulation to have taken place during the rise.

We recently reported the artificial production of typical temperature curves in young women in whom the ovaries were removed for disease of the pelvic organs and in women with complete ovarian failure. Estrogens administered provoked no change in the level of the temperature but the introduction of progesterone was followed by a prompt rise in the level and its maintenance during the period of administration of this progestational hormone. These experiments provided further data as to the hormonal mechanism of these temperature fluctuations in women.

DR. PHILIP F. SCHNEIDER.—This presentation has been particularly interesting to me, and quite stimulating. Dr. Cooperman has approached it from the angle of temperature change. He has brought out certain points that I think are very significant. In a considerable experience with endocrine therapy I have become convinced that progesterone is the secondary hormone of the ovary, and that estrogen is the primary one. The reason that these fertility cycles occur in patterns is distinctly due to the estrogen. I would like to cite one case.

I saw a patient in September, 1935, who had come into the hospital originally in June, having missed her period by five days, and started hemorrhaging. The diagnosis of incomplete abortion was made. She was curetted, and instead of decidual tissue, a cystic glandular hyperplasia was found. We are all aware of the dictum that glandular hyperplasia is due to the unopposed action of estrogen. After curettage and the microscopic diagnosis, the patient was placed on antuitrin S, according to the suggestions of Novak. Five or six weeks later she was brought into the hospital again, hemorrhaging. She was curetted again, with the same findings of cystic glandular hyperplasia. Following her second curettage, she was placed on progesterone, with the same result, that in five or six weeks, bleeding again started. The patient was a woman of 32, with two children, and with a normal-sized uterus. Hysterectomy was contemplated at this time. This was not carried out, and at my suggestion the patient was put on estrogenic therapy, with the result that the bleeding stopped within ten to twelve days.

Approximately six weeks after the bleeding stopped, a biopsy was taken and an endometrium was found that was still slightly cystic, but beginning to simulate a proliferative endometrium. Three weeks later, after continued estrogenic therapy, a period occurred. Twenty-eight days later, another period occurred, starting abruptly, lasting four days, and stopping abruptly. Preceding the third menstrual period, an endometrial biopsy was taken and secretory endometrium was found, demonstrating that ovulation had occurred. This had all occurred as a result of estrogenic therapy only. On the basis of supplying estrogenic substance, a normal menstrual cycle was produced.

On checking the patient two years later, it was found that pregnancy had occurred within three or four months after the last biopsy was taken. Patient went through the pregnancy uneventfully, and delivered a normal child at term. Within six or eight weeks after delivery, the same continuous excessive bleeding occurred, and a vaginal hysterectomy was done. On checking the tissue and the laboratory report, it was found that the uterus had been normal in size, with no abnormality except the cystic glandular hyperplasia. This evidence would seem to indicate that undoubtedly the anovulatory bleeding occurring in adolescent girls is possibly also due to a deficient supply of estrogenic substance by the ovaries.

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Discussion

DR. JOHN W. HUFFMAN.—A woman's life is commonly divided into childhood, adolescence, maturity, postmaturity, and senility. Childhood and adolescence are stages in development. Adolescence is properly subdivided into two phases, the first, one of adolescent sterility during which menstruation without ovulation occurs, the second, one in which, although sexual growth is continuing, conception and reproduction are possible. It has been well demonstrated (Montagu's monograph, "Adolescent Sterility," brings together most of the source material) that in most mammals puberty and the power to procreate are not synchronous events but that puberty is separated from fecundity by a considerable interval of time during which the individual is functionally sterile.

Dr. Cooperman's observations are interesting additional evidence substantiating the presence of a period of adolescent sterility. He is to be congratulated on the cooperation of his young co-workers. It must have taken much effort to maintain the interest of these young persons in a scientific project over a period of six years; I sincerely envy their parents their control over their adolescent offspring. I wish that Dr. Cooperman had records of many more subjects for it is well known that all chronologically adolescent girls are not sterile. There are many authenticated case records of pregnancy occurring immediately after puberty, and sometimes in these individuals puberty has occurred at an extremely early age. There is no question but that most women are incapable of conception for some months after the onset of menstruation but the variability in human beings, due to the differences in developmental age, is so great that conclusions drawn from only two subjects cannot help being subject to question.

There is general acceptance of the belief that certain changes in a woman's basal temperature are indicative of ovulation. I have not been as fortunate in obtaining satisfactory results with basal temperature charts as have many of those reporting in the literature. It is exceptional for me to see a typical ovulatory or anovulatory curve. Most of the charts patients bring to me are either similar to the ones Dr. Cooperman has designated as adolescent curves or else are so irregular that, while a cyclic rise and fall in temperature can be made out, the fluctuations are not regular nor clean-cut enough to foretell the date of ovulation.

The temperature curves are valuable when they give concrete evidence of ovulation. I shall continue to use them because of the occasional one that is helpful.

DR. M. EDWARD DAVIS.—We have had considerable experience with the use of body basal temperature records in the endocrine and sterility clinic and have found it a very useful tool for the study of ovarian activity. In a recent study of over 500 temperature graphs prepared by these patients, at least three of every four provided useful information. A few patients lead very irregular lives, working, eating, and sleeping at odd hours, so that these abnormal physical, metabolic, and nervous stimuli mask the hormonal control of basal temperature fluctuations.

Results

Fig. 1 summarizes the results in these 164 cases of toxemias of pregnancy. In the first group there are 75 hypertensive toxemia patients, in most of whom capillary fragility was determined once. A few were studied from two to five times during their pregnancy and early postpartum period. The group is subdivided into "mild" and "severe" hypertensive, depending upon their blood pressure, laboratory and clinical findings. Fifty-four were classified as

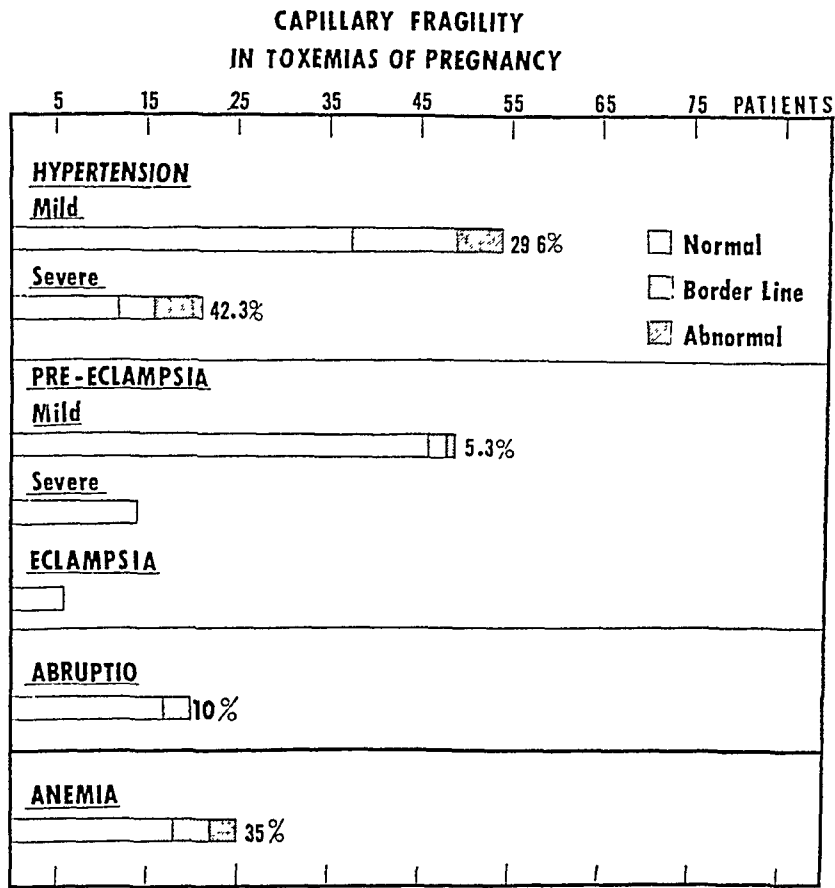


Fig. 1.

mild hypertensive; of this group, 29.6 per cent showed abnormal capillary fragility, 20.4 per cent of which were borderline, and 9.2 per cent definitely abnormal. In the severe hypertensive group of 21 cases, 42.3 per cent showed abnormal capillary fragility, of which 23.8 per cent were borderline and 18.5 per cent definitely abnormal. For the entire group, mild and severe, the total per cent of abnormal capillary resistance was 33.3 per cent. This is higher than the percentage reported by other investigators. Pregnancy might be a contributing factor, since some of the patients were normal to start with and the capillary resistance became abnormal as the gestation advanced. This brings out another point, that is, although in the severe hypertensive group the percentage was higher, abnormal fragility does not depend on the duration and the severity of the hypertension as Griffith has pointed out. Among the patients who showed normal capillary resistance, some had a history of hypertension of long duration. On the other hand, among the group that showed abnormal

CAPILLARY FRAGILITY AND THE USE OF RUTIN IN TOXEMIAS OF PREGNANCY*

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RECENT studies on hypertensive patients have shown that approximately 18 per cent of them have an abnormal capillary fragility.^{1, 2} We are interested in this condition because hypertension of varying degrees is found in over 8 per cent of our pregnant patients (pre-eclampsia, eclampsia, essential hypertension, and nephritis).³ Approximately two-thirds of the patients who have an abruptio placentae before labor have an essential hypertension and, since the disease is characterized by the extravasation of blood between muscle fibers and beneath the visceral and parietal peritoneum, we wish to know if the primary hemorrhage is related to an abnormal capillary fragility. If the latter were found to be present, prophylactic treatment with rutin would be indicated.

Rutin, a rhamno-glucoside of quercetin, is a flavon derivative and its formula is very much like hesperidin. Hesperidin has been shown by Szent-Györgyi,⁴ and later by Scarborough,⁵ to have a beneficial effect on abnormal capillary fragility and since then has been used on such cases. A number of investigators have reported on the efficacy of rutin since Griffith⁶ reported on 14 cases in 1944. This substance seems to be most promising in the treatment of increased capillary fragility,^{6, 7, 8} in the thiocyanate therapy of hypertensive patients,^{1, 7} in the hereditary hemorrhagic telangiectasia and in pulmonary and gastrointestinal bleeding of unknown origin,^{7, 8} and perhaps in allergy.^{7, 9} Rutin is preferred to hesperidin because it is more effective in smaller doses and so far no toxic symptom has been noted in laboratory animals or in patients.

Material and Method

A total of 164 cases of toxemias of pregnancy have been studied. In these patients both the positive pressure, Göthlin's Index,^{10, 1} and the negative pressure, Hecht-Dalldorf^{11, 12} tests were used. In normal individuals, the Göthlin's Index varies between 0 to 8 petechiae, 13 or more is considered abnormal, 9 to 12 is taken as borderline but still belongs to the abnormal group. In the Hecht-Dalldorf test, one or two petechiae at a certain negative pressure is considered the capillary resistance of that individual. One or two petechiae with a negative pressure of 20 to 25 cm. of mercury is considered normal.

In a high percentage of the cases, the two tests gave parallel results. In a few instances, the negative pressure test showed abnormal while Göthlin's Index was still in normal ranges. When capillary fragility was determined at a later date on the same patients, both tests were found abnormal.

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fragility was still normal. At 27 weeks, the patient came in with vaginal bleeding and delivered a stillborn baby. On admission, the capillary fragility was normal. On her postpartum visit seven weeks later, the capillary resistance was still normal.

Thirteen pregnant women with abnormal capillary fragility were given rutin. The patients were started with 20 mg. of rutin three times a day and the fragility determined at intervals of three weeks. If no improvement was noted at the end of the first three weeks, the dose was doubled. After the capillary fragility index returns to normal ranges, the patients take 20 mg. three times a day until delivery. In pregnant hypertensive patients whose capillary fragility is abnormal, 60 mg. of rutin a day is insufficient, since in almost every case the dose had to be increased to 120 mg. per day. No toxic symptoms were observed with the amounts given. A few patients were given ascorbic acid in conjunction with rutin. We were unable to demonstrate any vitamin C deficiency in toxemias of pregnancy.¹³

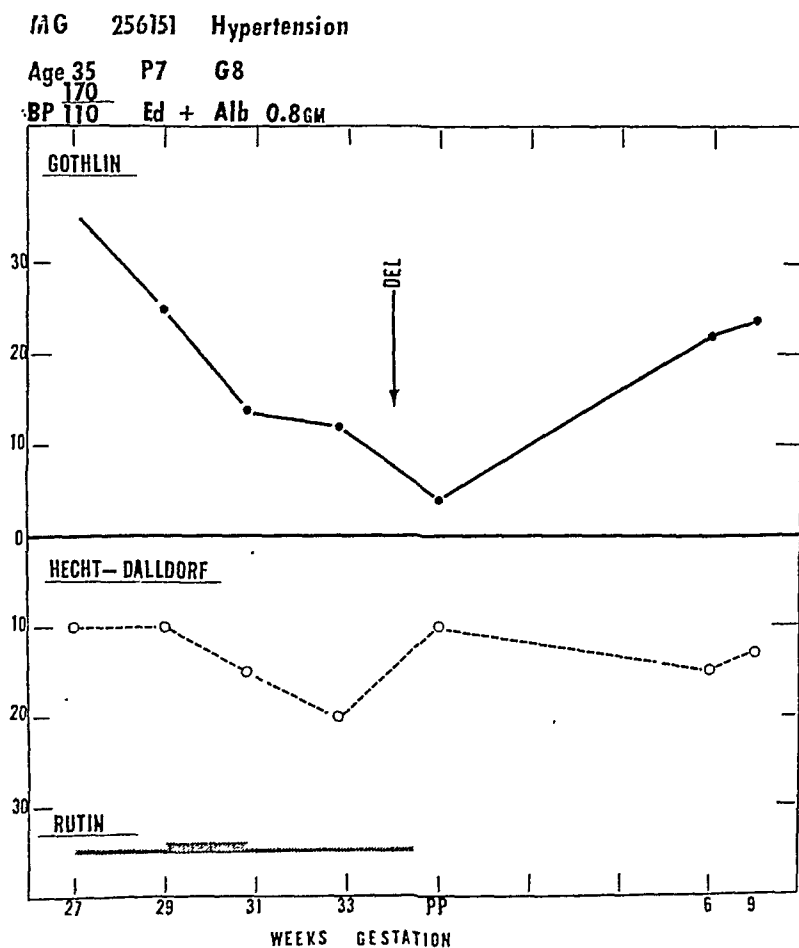


Fig. 3.

Of the 13 patients, two have not delivered. Twelve patients gave fair to good results. Fig. 3 is illustrative of one of these patients.

CASE 1.—M. G., No. 256151, a 42-year-old para vii, gravida viii, had hypertension with her last pregnancy in 1941. During this pregnancy, her blood pressure ranged between 148/84 and 190/100, proteinuria of 0.38 grams per 24-hour period and edema one plus. At 27 weeks' gestation, the capillary fragility showed marked abnormality. The patient was put on rutin, 20 mg. three times a day. Two weeks later another determination was done and the index was still high. Rutin was increased to 40 mg. three times a day. At 31 weeks' gestation, the capillary resistance was normal and rutin was reduced to 60 mg. per day.

capillary fragility, the blood pressure rise appeared in the latter part of the pregnancy. In this group, there were four patients with hypertensive encephalopathy, three of whom had a cerebral hemorrhage. The capillary fragility was borderline in two cases and normal in one. The fourth patient with clinical evidence of vascular spasm of the cerebral vessels had normal capillary fragility.

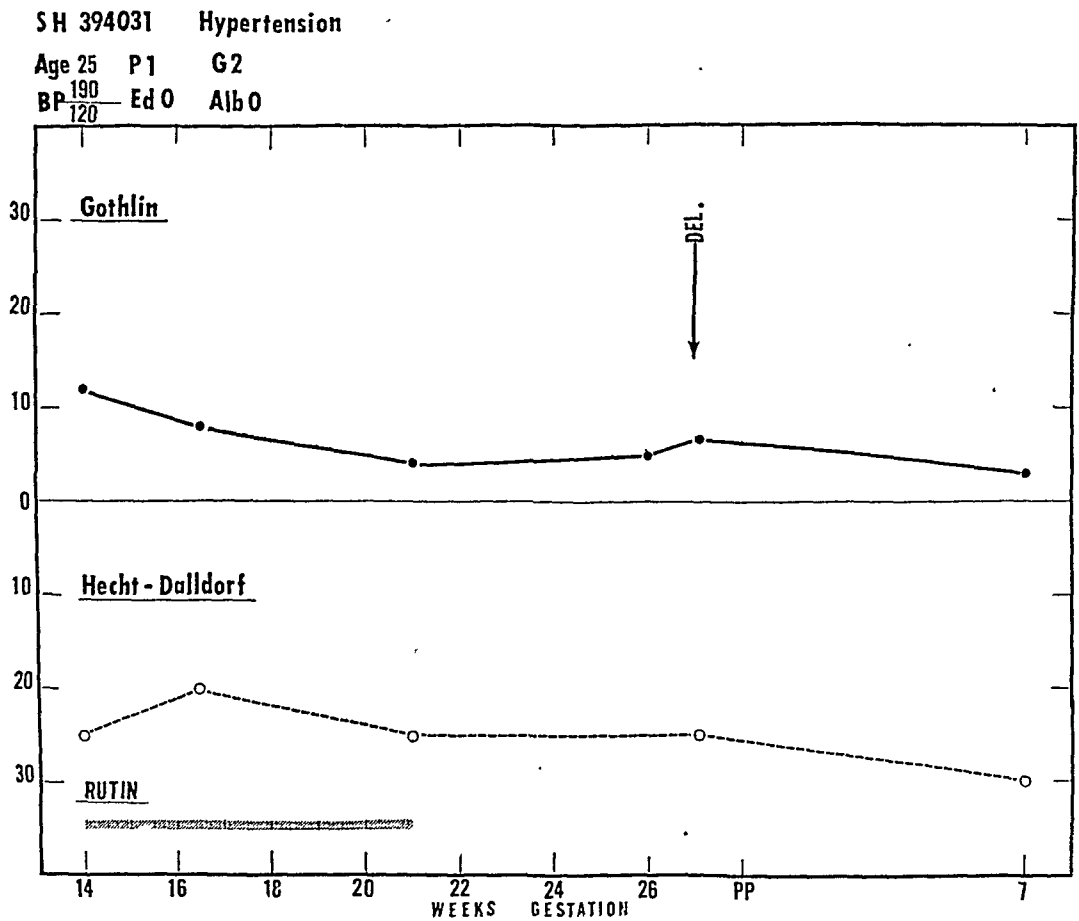


Fig. 2.—Göthlin scale indicates the sum of the number of petechiae occurring at 35 mm. of mercury pressure multiplied by two, and the additional number occurring at 50 mm. The Hecht-Dalldorf scale indicates the negative pressure in centimeters of mercury at which petechiae first appear.

The second group of patients had pre-eclampsia. A total of 63 patients was studied, of these 49 had mild pre-eclampsia and the remaining 14 were severe cases. In the former group, three patients showed abnormal fragility, 5.3 per cent, but two of these patients had low cell volumes of 25 and 29 per cent on the day of the test. In Fig. 1 it is demonstrated that as high as 35 per cent of patients with anemia have abnormal capillary fragility. If this is taken into consideration, only one patient has an abnormal capillary resistance. This patient might have been hypertensive rather than pre-eclamptic. The rationale for this reasoning is the observations in the severe pre-eclampsia and eclampsia. None of the fourteen severe pre-eclamptics and the six eclamptics studied showed abnormal capillary resistance.

Twenty cases of abruptio placentae of varying severity have been studied. Only two patients, known hypertensives, showed borderline fragility. One of these cases is illustrated in Fig. 2.

This patient (H. S.), No. 394031, a known hypertensive, had borderline fragility at 14 weeks' gestation. She was given 20 mg. rutin three times a day. At 22 weeks' gestation, her capillary resistance was normal and she was taken off rutin. At 26 weeks, the capillary

Thirty-three per cent of the patients who we thought had essential hypertension in pregnancy had an increased capillary fragility. The duration or the severity of the hypertension seemed to be of no significance. Pregnancy seemed to accentuate capillary fragility, possibly because of the relative or absolute anemia.

Capillary fragility was not increased in patients who were thought to have preeclampsia, if the anemia was excluded.

Abruptio placentae does not seem to be associated with an abnormal capillary fragility.

Rutin was used in 13 patients, in 12 of whom it was found efficacious in reducing the increased capillary fragility.

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Ten days later, the index was borderline with Göthlin and normal with Hecht-Dalldorf tests. At 34 weeks, the pregnancy was terminated by cesarean section, the patient delivering a 2,145 Gm. male infant. After delivery, no more rutin was administered. Eight days post partum, the Göthlin's Index was normal and the Hecht-Dalldorf test abnormal. At six and ten weeks post partum, the capillary fragility was found abnormal with both tests.

One patient not only did not respond but actually became worse in spite of the rutin.

CASE 2.—W. P., No. 411478, a 21-year-old para 0, gravida i, was first seen at 17 weeks' gestation. Clinical and laboratory findings were normal and the patient was placed on routine prenatal care. On her next visit, the blood pressure was 150/94. At 23 weeks' gestation, the capillary fragility was normal with Göthlin's Index and abnormal with the Hecht-Dalldorf test. At 33 weeks' gestation, the capillary fragility was borderline and the patient was given 120 mg. of rutin daily. At 36 weeks, the fragility was definitely abnormal.

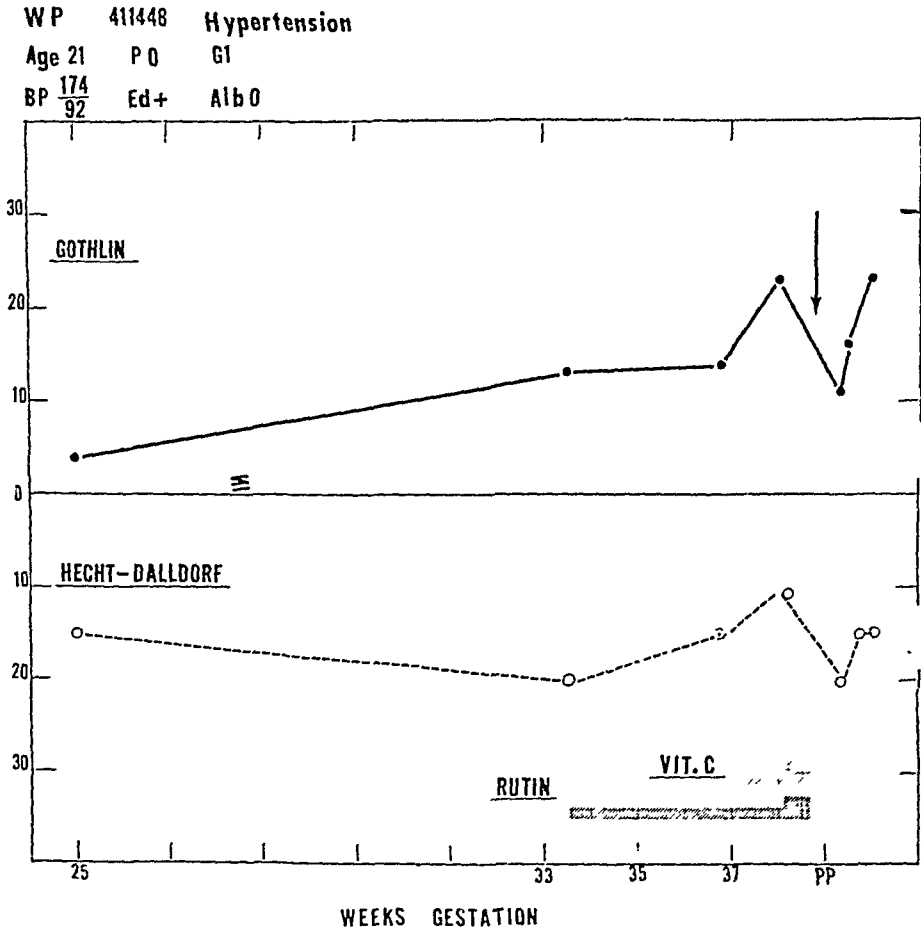


Fig. 4.

Vitamin C was also administered. At 37 weeks, the patient's blood pressure was 174/92, and her capillary resistance very much lowered. Both rutin and vitamin C were increased to 200 mg. a day, but two days later the patient went into labor and delivered a live female infant of 2,895 Gm. The capillary fragility was determined during the early postpartum period and was found abnormal. Fig. 4 illustrates the results in this patient. In this instance, rutin at the dose given had no effect.

Summary

The capillary fragility, using both the positive and negative pressure tests, has been studied in 164 cases of toxemia of pregnancy.

TABLE I. CASES IN RECENT LITERATURE

AUTHOR	YEAR	GR. VIDA	AGE	DURATION OF PREGNANCY		OUTCOME
				EXTRA-UTERINE	INTRA-UTERINE	
King	1942	iv	33	2 months	"near term"	Rt. tubal abortion. Bilateral salpingectomy. Spontaneous delivery of living child. Mother recovered.
Lawrence and Elsmore	1943	iv	32	3 months	Term	Ruptured left tubal pregnancy. Left salpingo-oophorectomy. Spontaneous delivery of living term child. Mother recovered.
Horchler	1944	-	-	2 months (Bilateral tubal)	3 months	Bilateral tubal pregnancies removed at 2 mos. Patient aborted intrauterine pregnancy 1 month later. Mother recovered.
Andwandter and Rodriguez	1938	vii	33	6 weekst	2 months	Ruptured left tubal pregnancy followed by dilatation and curettage for incomplete abortion. Mother recovered.
deMoraes Lene	1942	ii	29	3 weeks	Term	Unruptured early right tubal pregnancy. Intrauterine pregnancy continued to term. Spontaneous delivery of living child. Mother recovered.
Rabago	1943	viii	32	7 months	7 months	Laparotomy with removal of living extrauterine fetus and cesarean section for a living intrauterine fetus. Both lived 2 weeks. Mother recovered.
Howard	1943	i	28	2 months	7 months	Ruptured left ectopic pregnancy. Left salpingo-oophorectomy. Spontaneous delivery of living child at 7 months. Mother recovered.
Kohn and Burchard	1945	v	30	12 weeks	Twins—8 months 5 months	Cesarean section for twin pregnancy, 8 months (stillborn) and 5 months (macerated). Left salpingo-oophorectomy for unruptured tubal pregnancy at time of section. Mother recovered.
Collier	1946	iv	38	2 months—	6 weeks	Dilatation and curettage for incomplete abortion. Bilateral salpingo-oophorectomy and hysterectomy for twin pregnancy of the tube one month later.
Belson	1945	iv	35	6 weeks	24 weeks	Removal of left unruptured tubal pregnancy. Delivered fraternal twin intrauterine pregnancy. Mother recovered.
Gruenewald	1945	vi	41	6 weeks	Term	Ruptured right tubal pregnancy. Right salpingo-oophorectomy. Spontaneously delivered living child. Mother recovered.
Powell	1945	i	25	2 months+	Term	Ruptured left tubal pregnancy. Left salpingo-oophorectomy. Spontaneous delivery of living child intrauterine. Mother recovered.
Acosta-Sison	1945	x	30	1 month	3 months	Right tubal abortion. Right salpingectomy. Aborted intrauterine fetus 1 month later. Mother recovered.
Michaels	1938	v	25	4½ months	3 months	Aborted intrauterine fetus. Left tubal pregnancy removed at laparotomy. Mother recovered.
Michaels	1943	ii	32	3 months	6 months	Patient expired from cerebral hemorrhage. Combined extrauterine and intrauterine pregnancy found at autopsy.
Michaels	1946	v	35	6 weeks	3 months+	Ruptured right tubal pregnancy. Right salpingo-oophorectomy. Aborted intrauterine pregnancy. Mother recovered.
Michaels	1947	iii	34	1 month	8 months+	Right tubal abortion. Right salpingo-oophorectomy. Cesarean section delivery of living intrauterine fetus. Mother recovered.

COMBINED EXTRAUTERINE AND INTRAUTERINE PREGNANCY

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COMBINED extrauterine and intrauterine pregnancy is an unusual obstetric complication. It is well to keep in mind the difference between combined and compound extrauterine and intrauterine pregnancy. The former connotes the existence of simultaneous pregnancies, whereas the latter term refers to the superimposing of an intrauterine pregnancy on a previously existing extrauterine pregnancy, usually a lithopedion.

Duverney,¹ in 1708, is generally credited with the first description of the combined type. Since this observation, several cases have been reported. A survey of the literature calls one's attention to the confusion in proper classification and overlapping of collected case reports. In 1940, Bernstein,² excluding the obvious compound type, collected 294 authentic cases. Ludwig³ reviewed the literature through 1938 and reported a total of 352 cases. He did not, however, differentiate between combined and compound types. Mitra,⁴ in 1940, stated that there had been not more than 304 cases of combined extra- and intrauterine pregnancy reported in the world literature. Studdiford and Speck,⁵ in 1944, found 18 cases not included by Mitra and by combining these figures arrived at a total of 322 cases (they apparently did not include Mitra's two cases).

A review of the literature from the time of Studdiford and Speck's report in 1944 through October, 1947 reveals thirteen instances of combined extrauterine and intrauterine pregnancy.⁶⁻¹⁸ To these, I wish to add one case of my own, and three other previously unreported cases from the Charity Hospital of Louisiana at New Orleans. This brings the total number of reported combined pregnancies to 341.

The 17 cases included in this paper were productive of nine living children born near or at term. In one instance, both the intrauterine and extrauterine fetuses were delivered living. There was one maternal death.

The patients who have been carried to term are not numerous. Gemmell and Murray¹⁹ collected 81 cases which terminated in living fetuses. Morse,²⁰ in 1939, reported that there were 86 patients (including his own) who went to term and who were delivered of living babies.

The treatment of this condition is surgical, the majority of cases coming to the surgeon's attention early in pregnancy because of tubal abortion or rupture. It is in this type of case that the intrauterine pregnancy has the most favorable outcome. Unfortunately, the correct preoperative diagnosis is made in only four per cent to 9.3 per cent of cases.²¹ When a diagnosis of a combined pregnancy is established or even suspected at operation, every precaution should be exercised to preserve the intrauterine pregnancy, especially if a single corpus luteum is excised. Several cases are on record where the extrauterine pregnancy has

larged to the size of a three months' pregnancy and the author believed he could palpate a fetus within the uterine wall. Despite the presence of a corpus luteum in the right ovary, a right salpingo-oophorectomy was deemed necessary because the presence of adhesions and friable tissue precluded the possibility of salvaging the ovary.

Pathologic Report.—Tube contains clotted blood and placental tissue. Ovary contains corpus luteum and few follicular cysts.

The patient was placed on progesterone, stilbestrol, vitamin E, and thyroid postoperatively. Convalescence was uneventful. Sutures were removed on the tenth postoperative day.

Follow Up.—June 6, 1947: Uterus enlarged to a three and a half or four months' pregnancy. No cramps or bleeding. July 25, 1947: History of twins on both sides of the family. Blood pressure 128/80, weight 120 pounds. Vertex right occipitoanterior, fetal heart tones 150 right lower quadrant. Pelvic: intraspinous 20 cm., intercrestal 23 cm., external conjugate 17.5 cm., diagonal conjugate 11.5 cm., conjugata vera 10 cm., sacrum curved, transverse outlet 8 cm., posterior sagittal outlet 7.5 cm. *Impression*, generally contracted pelvis, borderline.

On Oct. 14, 1947, patient was readmitted to the hospital because of signs and symptoms of mild toxemia of pregnancy. She responded well to bed rest, ammonium chloride, and mild sedation. Hematocrit was 28. Sickling preparation negative in twenty-four hours. Blood urea nitrogen 6.3. Serum proteins 6.51. Kline and Kolmer tests were negative. Rh positive, type O. On Nov. 3, 1947, a transfusion of 500 c.c. of whole blood was administered and a count later in the day revealed 11.0 Gm. hemoglobin, 4.3 million red blood cells, 6,200 white blood cells with 65 per cent polymorphonuclear leucocytes and 35 per cent lymphocytes. On Nov. 3, 1947, the height of the fundus measured 39 cm. An elective section was scheduled for the next day. The patient began to have regular uterine contractions at 1:30 P.M. on Nov. 4, 1947, and cesarean section resulted in the delivery of a healthy, 6 pound, 7 ounce male infant. There were no adhesions present at the site of removal of the previous right tubal abortion. No corpus luteum was noted in the left ovary. Five hundred c.c. of blood were administered during the operation. Recovery was uneventful and the patient and her baby were discharged on the tenth postoperative day.

Comment.—This case is representative of the usual chain of events which is seen in this condition. The onset of initial symptoms coincided with the suspected date of tubal abortion. The diagnosis of coexistent extrauterine and intrauterine pregnancy was made at the first operation. Despite removal of the corpus luteum in the right ovary, the patient progressed to term. The use of stilbestrol and progesterone postoperatively probably helped prevent abortion. Cesarean section resulted in the birth of a normal, healthy, 6 pound, 7 ounce boy at or near term.

CASE 2.—F. V. (T46-247314), Negro, aged 35 years, was admitted to Charity Hospital on Dec. 22, 1946, complaining of acute abdominal pain. Gravida v, para v, last pregnancy, 1944. Menstrual periods were noted to occur every 28 days, lasting 3 to 4 days. Last normal menstrual period occurred Oct. 25, 1946, and lasted for three days. On Nov. 28, 1946, scanty menses started and the patient spotted almost daily until time of admission. On Dec. 17, 1946, she developed intermittent, colicky pain in the lower abdomen and on Dec. 20, 1946, while in bed, was seized with a sudden severe cramping pain which in a short period of time radiated to the right shoulder and epigastrium. An evacuation of the bowels failed to relieve the pain. Thirty minutes later she vomited and the abdomen gradually became distended and tender.

On examination, the patient was found to be an obese, well-developed, and well-nourished woman who appeared acutely ill. The mucous membranes were pale, temperature 100.4° F., pulse rate 120, respirations 20, and blood pressure 140/80. The abdomen was distended and generally tender. Maximum rebound tenderness was found in the right lower quadrant, and a few peristaltic sounds were present.

Pelvic examination revealed the following findings; vagina cold; cervix soft, admitting tip of finger, tender on motion; corpus believed to be slightly enlarged, soft, and retrodisplaced; bilateral adnexal tenderness but no masses. Rectal examination revealed a boggy mass in the

continued to progress along with the intrauterine pregnancy. This type of case poses a difficult approach to treatment and each case must be handled as an individual problem. Novak²¹ reviewed nine cases in which both the extrauterine and intrauterine pregnancies progressed to term, and the fetuses were delivered alive.

The maternal mortality rate is surprisingly high. Gemmell and Murray,¹⁹ in collecting 217 cases, noted that the series mortality rate amounted to 14.4 per cent if autopsy cases were excluded. Perhaps the more frequent employment of cul-de-sac puncture in suspected cases of tubal abortion or rupture would lead to earlier diagnosis of extrauterine gestation and, therefore, to early and prompt treatment. Replacing blood loss with immediate blood transfusions and the employment of sulfonamides and antibiotics to combat infection should aid materially in the reduction of maternal mortality. We believe it unwise to attempt removal of the placenta in abdominal pregnancy.

Report of Cases

In addition to the author's case (Case 1), a search through the records of the Charity Hospital of Louisiana at New Orleans for the last ten years produced but three additional authentic cases of combined extrauterine and intrauterine pregnancy. Since these latter three cases were not previously reported, they will be included in this paper. During the same period, Beacham²² found 377 instances of ectopic gestation. The ratio of combined extra- and intrauterine pregnancies to ectopic is therefore slightly less than 1 per 100. This is in keeping with Martin and Meyer's²³ estimate of the occurrence of combined extrauterine and intrauterine pregnancies as 1 in 105 ectopic pregnancies.

CASE 1.—First admission. V. J. (T45-191515), Negro, aged 32 years, was admitted to Charity Hospital on May 1, 1947, complaining of lower abdominal pain and vaginal spotting. Menses had begun at 13 years, occurred every 28 to 30 days, and lasted four days. Her last normal period was believed to have occurred Feb. 16, 1947. She commenced to bleed vaginally on March 15, 1947, and continued to spot almost daily. Coincident with this, she complained of the onset of vague lower abdominal pains, most marked in the right lower quadrant. Four days prior to admission, the pain became worse and radiated to the right lumbar region. Nausea and vomiting had occurred during the onset, but had not been troublesome since. Obstetric history: gravida iii, para iii: 1935, forty-hour labor, difficult forceps delivery, dead baby; 1936, classical cesarean section for fetopelvic disproportion resulting in living 6 pounds, 8 ounce child; 1938, low cesarean section resulting in delivery of 8 pound, 7 ounce living baby. Stormy postoperative course.

On examination, the temperature was 100° F., pulse rate 88, respirations 18, and blood pressure 114/96. The patient did not appear acutely ill. Abdominal examination revealed the presence of supra- and infraumbilical scars. The abdomen was slightly distended and generally tender. Peristalsis was active and an orange-sized, ill-defined mass was thought to be present in the right lower quadrant. Pelvic examination revealed the following findings: no increase in vaginal heat, slightly softened cystic cervix, moderately tender on motion, with a small amount of bright-red blood issuing from the external os. Corpus was enlarged slightly, anteriorly placed, and mobile. An orange-sized, tender, cystic mass was present on the right, and the left adnexa was believed to be normal. No cul-de-sac fullness was noted. Catheterized urine specimen was negative. Hematocrit 23, sedimentation rate 31 corrected, white blood cells 15,000, 78 per cent polymorphonuclear leucocytes. Cul-de-sac puncture produced no old blood or exudate.

Impression.—Right tubal abortion with moderate intra-abdominal bleeding. At operation, when the peritoneal cavity was entered, approximately 800 c.c. of old clotted blood was found. There was no active bleeding. Intra-abdominal examination revealed normal-appearing left adnexa with an old tubal abortion present on the right. The uterus was soft and en-

on manipulation of the cervix, but the cul-de-sac felt full and soft. Muscular weakness of the left upper and lower extremities was noted. *Impression*, Possible extrauterine pregnancy; hypertensive cardiovascular disease; generalized lues.

On May 16, 1943, an x-ray of the abdomen was reported as showing a fetus of approximately six months' gestation. On May 18, 1943, the patient was assisted to the bathroom, and on returning complained of pain in the back and abdomen. She immediately became comatose and expired in a matter of a few minutes.

Autopsy Report.—The uterus measured 21 by 18 by 9.5 cm. and contained a fetus weighing 650 Gm. Attached to the right side of the uterus and to its rear is a mass measuring 9 by 12.5 by 7 cm. This mass is dark red and soft. The cut surface of this mass reveals a double lumened cavity containing in its inner cavity a macerated fetus measuring 10.8 cm., crown to rump. The other cavity contains dark clotted blood. The patient apparently expired due to a massive cerebral hemorrhage.

Comment.—While clinically the supposition that an extrauterine pregnancy existed was entertained, the patient was treated conservatively only to expire from a cerebrovascular accident a few days after her last admission. The early diagnosis of extrauterine pregnancy might have been substantiated by a cul-de-sac puncture on her admission March 9, 1943. Apparently the intrauterine fetus was viable and might well have progressed to term had the patient lived.

CASE 4.—First admission. D. B. (T38-43675), Negro, aged 25 years, was admitted to Charity Hospital on May 5, 1938, complaining of weakness and severe abdominal pain. She was a gravida v, para iii, who last delivered six months prior to this admission. She nursed her baby for three months, and the last normal menses occurred on Jan. 28, 1938, to Feb. 2, 1938. Three weeks prior to admission she noted a gradual onset of cramping lower abdominal pain.

Physical examination revealed a well-developed, well-nourished, Negro woman who was not acutely ill. Temperature 102° F. Pulse rate 120, respiration 30, blood pressure 110/80. The abdomen was markedly distended and diffusely tender; however, no rigidity was noted. Pelvic examination revealed the following findings: relaxed perineum, increased vaginal heat, cervix chronically diseased and soft. An ill-defined mass was palpated, arising out of the pelvis. The adnexa were not identified. Urine, albumin O, sugar O, microscopically, few fine granular casts, occasional white blood cell. Hemoglobin 40 per cent, white blood cells 20,500, 85 polymorphonuclear leucocytes, 15 lymphocytes, smear for gonococci positive. *Impression*, acute pelvic inflammatory disease. Patient was treated with chemotherapy and on May 9, 1939, she spontaneously aborted a fetus and placenta.

Pathologic Report.—Specimen consisted of a fetus and placenta. The fetus measured 12 cm. in length.

The patient continued to maintain a septic course and was administered 500 c.c. of blood on May 21, 1938. Pelvic examination on May 25, 1938, revealed the uterus to be "enlarged to almost the umbilicus with several small fibroids." She was eventually discharged on June 14, 1938.

Second Admission. The patient was readmitted on July 19, 1938, much improved, with much the same findings as at the end of her previous admission. On July 22, 1938, a dilatation and curettage and laparotomy were performed. At operation, the surgeon, on entering the abdomen, discovered a pelvic mass situated in the midline and adherent to the peritoneum. This mass apparently arose from the left adnexa. A subtotal hysterectomy and bilateral salpingo-oophorectomy were performed. A large cystic mass was removed from the lower border of the liver.

Pathologic Report.—Cystic mass contained a fetus of approximately four and one-half months' duration surrounded by old hemorrhage.

Final diagnosis, tubal pregnancy, echinococcus (?) cyst of the liver.

Convalescence was uneventful and the patient was discharged on Aug. 1, 1938. Unfortunately she did not appear in the postoperative Clinic for follow-up.

cul-de-sac. A catheterized urine specimen was negative. Hemoglobin 8 Gm. hematocrit 23 per cent, red blood cells 2.66 million. Cul-de-sac puncture revealed presence of old blood. Preoperative diagnosis, ruptured tubal pregnancy.

The patient was taken to the operating room and a transfusion started. When the abdomen was entered, approximately 1,000 c.c. of old and fresh blood were encountered. Inspection of the pelvic viscera revealed normal-appearing left adnexa. The right tube presented a freely bleeding ragged opening in the distal one-third. Right salpingo-oophorectomy was done (a torn right infundibulopelvic ligament apparently necessitated the removal of the ovary as well as the tube). One of the surgeons remarked that the uterus appeared to have a pregnancy within. A total of 1,500 c.c. of blood were administered.

Pathologic Report.—Tube, chorionic villi present, hemorrhage, necrosis, and acute inflammation; ovary, corpus luteum present.

The patient was not put on any special medication and had an uneventful convalescence, going home on the eighth postoperative day.

Follow-up.—Feb. 14, 1947: On Jan. 15, 1947, the patient had severe cramps and bleeding, and passed a completely formed fetus, 7 to 8 cm. in length with cord and placenta. May 9, 1947: Uterus normal size. Patient discharged.

Comment.—This case was typical of a ruptured ectopic pregnancy. Cul-de-sac puncture was positive. She received early and prompt surgical treatment. Though one of the surgeons suspected that the uterus might contain a fetus, no special therapy (stilbestrol, progesterone, etc.) was administered. Since the pathologist reported a corpus luteum present in the removed ovary, one is led to believe that since the pregnancies were at an early stage its absence may have led to abortion of the intrauterine fetus. Large doses of estrogens and progesterone may have tided over the critical period, and the patient may possibly have gone to term.

CASE 3.—M. O. (I43-83883), Negro, aged 32 years, was admitted to Charity Hospital on May 14, 1943. She was gravida ii, para ii, her last child having been born in 1940. At this time she was noted to have had a severe toxemia. She had received one injection of bismuth salicylate in 1941. Patient appeared at this hospital on March 9, 1943, complaining of cramping pains in the lower abdomen of one week's duration. At this time, her last menstrual period was Nov. 31, 1942. In December, 1942, she had no menstrual period; in January, 1943, she spotted a small amount; and, in February, again did not menstruate. She complained of a sudden onset of cramping lower abdominal pains which would last ten minutes, and occurred approximately every 10 to 15 minutes.

Physical Examination revealed blood pressure 152/96, pulse rate 140, temperature 99.6° F. She was well developed and well nourished and appeared acutely ill. The positive physical findings at this time were a slight cardiac enlargement to the left, slight abdominal distention, and an orange-sized mass was palpated to the left of the midline. Tenderness and rebound tenderness were present in the lower abdomen.

Pelvic examination revealed the cervix to be displaced upward, and the cul-de-sac felt full and boggy. The impression at this time was a possible ruptured ectopic pregnancy versus tuboovarian abscess. An x-ray of the lower abdomen on March 23, 1943, revealed a large oval area of increased density extending from the third lumbar vertebra to the pelvis. No evidence of a fetus could be made out, but the ascending colon was displaced to the right. Another flat plate of the abdomen taken on March 26, 1943, was reported as suggesting a fetus in the pelvis. During this admission, she had a red blood cell count of 1.9 million with 22 per cent hemoglobin. Kline and Kolmer tests were strongly positive. She remained in the hospital under observation until April 1, 1943. Her final admission was on May 14, 1943, when she complained of weakness of her left arm and leg and swelling of the abdomen. Physical examination at this time revealed the blood pressure to be 160/90. The lower abdomen was distended, and fetal parts were questionably palpated in the left lower quadrant. Pelvic examination revealed the cervix to be displaced anteriorly. There was little tenderness.

OBSTETRIC EXPERIENCE IN A NAVY HOSPITAL*

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THERE is a widespread, and often well-founded, belief that the obstetric results of the small hospital, the military hospital, or the obstetric wing of a general hospital are less good than are those of the larger, one-purpose hospital. Therefore, it is incumbent on these smaller hospitals to subject themselves to periodic critical reviews in order to define and correct their deficiencies. This study is a review of the material and the results found in the Obstetrical Service of the U. S. Naval Hospital, Philadelphia, Pa., in 1946—a service that is small, military, and a part of a large general hospital. No statistical significance is claimed for the following figures. They are of interest only for the purpose of comparison.

During the year 1946, there were 614 women delivered of 618 babies, there being four sets of twins. There was no maternal mortality.

A study of the age groups indicates that Navy wives have their babies a little earlier in life than do other women. As shown in Table I, 67.5 per cent of our patients were less than 26 years old when delivered. The problems of the elderly nullipara and of the grand multipara were seldom encountered.

TABLE I. DELIVERIES BY AGE GROUPS

AGE IN YEARS	NUMBER OF PATIENTS	PERCENTAGE
16-20	112	18.2
21-25	303	49.3
26-30	136	22.1
31-35	54	8.8
36-40	8	1.3
41-45	1	0.16

The average number of days the patient remained in the hospital post partum varied a great deal from month to month, as shown in Table II. In the first half of the year the patient usually was out of bed on the seventh day and went home on the eighth. In April, her average stay was 9.2 days. In the latter third of the year earlier ambulation was instituted. The patient got out of bed on the fourth day and went home on the fifth. In September, the postpartum stay dropped to 5.5 days, and never rose to six days during the remainder of the year. No complications chargeable to early ambulation were noted.

TABLE II. POSTPARTUM DAYS SPENT IN HOSPITAL

MONTH	DAYS	MONTH	DAYS	MONTH	DAYS
Feb.	8.4	May	9.1	Sept.	5.5
Mar.	8.7	June	7.9	Oct.	5.8
Apr.	9.2	July	7.4	Nov.	5.9
		August	6.9	Dec.	5.7

*Presented at a meeting of the Philadelphia Obstetrical Society, Feb. 5, 1948.

Comment.—This case is a reversal of the usual findings. On her first admission, in addition to an acute specific salpingitis, she aborted a 12 cm. fetus. On her readmission two months later, a four and one-half months' tubal pregnancy was removed. A probable echinococcus cyst of the liver was also excised.

Summary

1. Four new instances of combined extrauterine and intrauterine pregnancy are reported.

2. The ratio of coexistent ectopic intrauterine pregnancy to ectopic pregnancy at the Charity Hospital during the last ten years is approximately 1 to 100.

3. At the time of operation for an ectopic gestation, one case (Case 1) was correctly diagnosed as a combined pregnancy and in one case (Case 2) this condition merely suspected. In both cases the corpus luteum was unfortunately sacrificed. Case 1 continued to term, and a living child was delivered by cesarean section, while Case 2 aborted twenty-four days postoperatively. In such instances, substitution hormonal therapy should be instigated and maintained at least to the twenty-fourth week.

4. In approximately 25 per cent of the reported cases in the literature, one or occasionally both fetuses continued to term.

5. The reported maternal mortality is high. The following factors should materially aid in its reduction:

A. More widespread use of cul-de-sac puncture as an aid in the early diagnosis of ruptured ectopic pregnancy.

B. Avoidance of removal of the placenta of the abdominal twin.

C. Liberal and prompt use of whole blood and plasma in the emergency stages.

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were done because of failure of the occiput to rotate anteriorly, two for cephalopelvic disproportion, one for inertia, one for constriction ring, and one for premature separation of the placenta late in labor. All of these ten babies survived, though one had an injury of the seventh cranial nerve. Of the twenty-one babies delivered by breech extraction, three did not survive. Two of them died in utero prior to the onset of labor and were so diagnosed on admission. The third died of tentorial tears with cerebral hemorrhage. Sixty-five and eight-tenths per cent of the patients who were delivered per vaginam had episiotomies.

TABLE V. METHOD OF DELIVERY

TYPE	NUMBER	PER CENT
Spontaneous	440	71.2
Low forceps	138	22.3
Midforceps	10	1.6
Breech extraction	21	3.4
Cesarean section	8	1.3
Version and extraction	1	0.16

The indications for cesarean section were varied, as shown by Table VI.

TABLE VI. INDICATIONS FOR CESAREAN SECTION

NUMBER	INDICATION
2	Placenta previa centralia.
1	Flat pelvis. Paranoia.
1	Severe, fulminating toxemia.
1	35-year-old nullipara, occiputoposterior, 19-hour labor with no progress, ruptured membranes.
1	Breech, generally contracted pelvis, large baby, 31-year-old nullipara.
1	Fetal distress due to short cord.
1	Previous section for cephalopelvic disproportion.

Operative procedures other than for delivery were few. Uterine packing was done only twice, manual removal of the placenta once, and labor was surgically induced four times. None of these procedures was followed by morbidity.

TABLE VII. OTHER OPERATIVE PROCEDURES

PROCEDURE	NUMBER	PERCENTAGE
Uterine packing	2	0.32
Manual removal of placenta	1	0.16
Surgical induction of labor	4	0.65

Complications of labor were not remarkable (Table VIII). There was one third-degree tear, and three tears of the cervix sufficient to warrant repair. Hemorrhage of over 500 c.c. occurred ten times, or in 1.6 per cent of the patients. Retained placenta was seen 3 times (0.48 per cent).

TABLE VIII. COMPLICATIONS OF LABOR

	NUMBER	PER CENT	LATER MORBIDITY
Third degree laceration	1	0.16	0
Cervical laceration, repaired	3	0.48	1
Hemorrhage over 500 c.c.	10	1.6	1
Retained placenta	3	0.48	0
Prolonged labor—over 24 hrs.	26	4.2	4
Membranes ruptured over 12 hrs.	17	2.8	1

For anesthesia, nitrous oxide, alone or in combination with ether, was the agent chosen for about two-thirds of the patients (Table III). Another one-fourth of them received ether alone. Pudendal block was found to be very satisfactory for the delivery of women with infections of the respiratory tract. Caudal anesthesia, effected by a trained anesthetist, was used twelve times but was not found to be suitable for general use in our patients. Spinal anesthesia was not used during the year in obstetrics. Practically all patients were given Demerol and scopolamine for analgesia. One patient developed bradycardia, which was thought to be due to the Demerol. She was given atropine, which did not relieve the bradycardia.

TABLE III. ANESTHETIC AGENTS

TYPE	NUMBER	PER CENT
Nitrous oxide, oxygen, and ether	350	57.0
Ether	156	25.4
Nitrous oxide and oxygen	40	6.5
Pudendal block	25	4.0
Caudal	11	1.8
Local infiltration	3	0.5
Local and ether	1	0.16
Caudal and local	1	0.16
Spinal	0	0.0
None	27	4.4

In interpreting morbidity, strict standards were observed (Table IV). Any patient whose temperature reached or exceeded 100.4° F. on any two days following delivery, excluding the first 24 hours, was considered morbid. Temperatures were taken five or six times a day. In patients in whom infection was both genital and extragenital, or in whom the site of the infection could not be determined, the morbidity was considered to be genital in origin. All pregnancies of twenty weeks or more were included. Adhering to these standards a morbidity incidence of 5.9 per cent was found.

TABLE IV. MORBIDITY AND ITS SOURCE

	NUMBER OF PATIENTS	PERCENTAGE INCIDENCE
Morbidity, total	36	5.9
Extragenital	14	2.3
Genital	22	3.6

Two and three-tenths per cent of the patients were considered to have extragenital causes for their morbidity. The remainder, 3.6 per cent, represent the true puerperal infections. One may view this figure with skepticism. Perhaps the series is too small for percentages to mean anything. Perhaps our patients leave the hospital before they have an opportunity to exhibit their morbidity. It is more likely, however, that an early attack with powerful therapeutic agents is reducing the morbidity rates. The urge to start the administration of penicillin or a sulfonamide or both to a patient who has shown one significant rise of temperature is just as strong in the Navy as it is in civilian practice. To find such a patient at morning sickcall, to see her complete her puerperium without another significant elevation of temperature, and to speculate on what her course might have been without that speedy treatment are not uncommon experiences.

Of interest also is a group of nine women who were known to have parametritis, endometritis, or abscess in the episiotomy, but who failed to meet the temperature requirements for morbidity.

Table V shows that 28.8 per cent of the deliveries were operative. There were no high forceps and no destructive operations. Of the ten midforceps, five

rest in the hospital and labor was induced surgically. One patient went into labor prematurely at 31 weeks and delivered a baby which died in its neonatal period. No other cardiac patient lost her baby.

An obstetric report is not complete without some information concerning the infants delivered. (Table X.) In this series, no infant weighed over ten pounds at birth. Twenty-seven of them (4.4 per cent) weighed less than five and one-half pounds. Two of the twenty-seven had died antepartum at 24 and 28 weeks. Three of the twenty-five prematures born alive died in the neonatal period. They were of 20, 24, and 30 weeks' gestation. Of the twenty-five prematures born alive, 88 per cent survived.

TABLE X. CONDITION OF INFANTS AT BIRTH

CONDITION	NUMBER	PERCENTAGE
Liveborn babies	611	98.8
Prematurely born	27	4.4
Injured at birth	4	0.6

There were seven stillbirths in the entire group of infants. This gives a liveborn incidence of 98.8 per cent. Four infants were injured at birth, for an incidence of 0.6 per cent. Two of the injuries were of the facial nerve and cleared up rapidly. One was a hemorrhage into the sternomastoid muscle, and it disappeared eventually. The fourth was tentorial tearing, with a fatal result.

Expressing certain facts (Table XI) in terms of live births has disadvantages, but for the sake of easy comparison two are given here.

TABLE XI. INFANT MORTALITY

	NUMBER	RATE PER 1000 LIVE BIRTHS
Stillbirths	7	11.4
Neonatal deaths	6	9.8

The stillbirth rate in our series was 11.4 per thousand live births, and the neonatal death rate was 9.8 per thousand live births.

In the literature of obstetrics are many studies of the obstetric results of our leading institutions. Most of them reflect painstaking care and honesty in their preparation. Newberger's three recent analyses of the obstetric activities of the entire state of Illinois are of great interest because of the large numbers involved. Comparison of our figures with those shown in similar studies indicates that it is possible for the small, military obstetric service to have results which compare favorably with those of well-regulated civilian institutions.

Discussion

DR. NEWLIN F. PAXSON.—The very excellent results that Dr. Smith presents are worthy of commendation. This is an example of what a full-time staff can do under the direction of a qualified specialist. We have been worrying about the possibility of government in medicine, and here we have an excellent example that it can produce excellent results and may easily be an argument for developing similar projects. I am interested to noted the high incidence of obstetric analgesia. At our institution, we have considerable trouble training the interns to give obstetric analgesia in every case. I noted that only seven of the total number failed to receive analgesia.

I was interested in noting that only one cervix was inspected and repaired. At Hahnemann, our policy has been routine inspection of all cervixes, with repair of all tears except the small ones. This is in the nature of cancer prevention. I think, if the policy of routine inspections of the cervix was followed, we might find a higher incidence of repairs.

Twenty-six patients, 4.2 per cent of the total number, were in labor over twenty-four hours. This reflects an unwillingness to interfere in a labor which is making some progress and shows no complication other than prolongation. These patients received supportive treatment and rest periods as indicated. The average length of labor in this group was 41 hours. Four, or 15.4 per cent, of these patients later showed morbidity. All of these 26 patients left the hospital with living and well babies except one. In that patient, the marginal one-fifth of the placenta separated prematurely late in labor and the baby could not be resuscitated after delivery.

In 17 of our patients (2.8 per cent) the membranes ruptured twelve hours or more prior to delivery. One of them (5.9 per cent) later exhibited morbidity. In one of them, there was an intrapartum fetal death of a child presenting by the face.

The complications of pregnancy are shown in Table IX. Placenta previa occurred four times. Two of the patients with this complication were delivered by cesarean section, one by low forceps, and one spontaneously. There were no fetal deaths associated with placenta previa. Premature separation of the placenta occurred eleven times. None of these hemorrhages was concealed or of a severe degree. Fetal death was associated with this diagnosis twice. One was an intrapartum death following separation of the marginal one-fifth of the placenta. The other death was due to immaturity, the patient being in the twenty-first week of her pregnancy.

TABLE IX. COMPLICATIONS OF PREGNANCY

CONDITION	NUMBER	PERCENTAGE
Placenta previa	4	0.65
Premature separation of placenta	11	1.8
Pre-eclamptic toxemia, mild	20	3.2
Pre-eclamptic toxemia, severe	2	0.32
Chronic glomerular nephritis	2	0.32
Hypertensive disease	1	0.16
Pernicious vomiting	2	0.32
Syphilis	4	0.64
Gonorrhea	1	0.16
Pyelonephritis	6	1.0
Rheumatic heart disease	7	1.1
Severe anemia	2	0.32

Twenty patients (3.2 per cent) had pre-eclamptic toxemia, mild. Two (0.3 per cent) had a severe pre-eclamptic toxemia. One of these had a fulminating type which, with her other findings, seemed to indicate delivery by cesarean section. No patient developed convulsions, and there was no fetal loss among the toxemia patients.

Pyelonephritis appeared in six patients (1 per cent). In one of these women, the fetus died in utero at 28 weeks. She went into labor spontaneously and delivered a macerated fetus.

Routine Kahn examinations showed four (0.64 per cent) patients to have syphilis. Each of these patients received eight million units of penicillin, followed by bismuth and Mapharsen. None of their babies showed evidence of congenital syphilis.

Rheumatic heart disease was found in seven patients (1.1 per cent). Two of these patients were Class 1 cardiacs, four were Class 2, and one was Class 3. The Class 3 patient and two of the Class 2 patients decompensated later in pregnancy or in labor. All patients with heart disease were under the joint care of cardiologist and obstetrician throughout pregnancy. They spent the last four to ten weeks of pregnancy in bed in the hospital. They were delivered per vaginam, under open-drop-ether anesthesia. They were allowed to go into labor spontaneously, with one exception. One patient developed a toxemia while on bed

A REPORT ON 159 THIRD DEGREE LACERATIONS

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DURING the period January, 1942, to July, 1947, there were 9,170 deliveries at this hospital, and 159 patients who delivered vaginally sustained third degree lacerations. There is an aura of catastrophe in the eyes of the house staff when this complication occurs. This feeling has led us to analyze our series of cases so that a proper perspective as to etiology, prophylaxis, repair, and sequelae may be attained.

Third degree tears are confusingly defined in the standard texts, and various clinics. Davis¹ describes it as follows: "If a tear extends through the sphincter ani into the rectum it is a third-degree laceration." DeLee² states that "when the sphincter muscle and anus are involved these are designated as third degree or complete lacerations." Stander³ describes the condition in the following manner: "In third degrees, the tear extends completely through the perineal body and the sphincter ani muscle, and for a certain distance up the anterior wall of the rectum. These are designated as complete in contradistinction to those of the first and second degrees—the incomplete tears in which the rectum is not involved." Curtis⁴ states "Tears are classified as complete or incomplete according to whether or not the external sphincter is involved." In a later text⁵ he clarifies it as follows: "Tears may be incomplete or may extend as far as the anus with destruction of the internal fibers as well as the external fibers, and some of the levator ani fibers which support the rectum. In the latter instance there is a complete laceration—" Wharton⁶ words the definition: "If a tear goes through the sphincter ani muscle it is a third degree tear. If it extends through the whole perineal body from vagina to the rectum (it may also extend into the rectum) it is a third degree tear." The *Standard Nomenclature of Disease*⁷ enhances the confusion by calling it "Laceration of the perineum involving the sphincter ani (complete tear)." In this area the three medical schools call involvement of any tissue deep to the sphincter capsule a third degree laceration. This paper defines a tear through or into the sphincter as an incomplete third degree tear, and those that enter the anus or rectum as a complete third degree. The division, because the latter involves an infected area and the former does not, is suggested for a standard classification.

Curtis and Anson⁸ point out that in an anatomic dissection of the perineum there is a tendency for the constituent elements to become intermingled. Muscular layers become aponeurotic or fascial. Ligaments fuse with coverings of large vessels and fascial coats of organs. However, the outer layers are mostly muscular. Martius⁹ divides the perineum into three layers. The innermost is the levator ani; the middle layer is the urogenital diaphragm; the outer layer is the sphincter muscle of the anus and anteriorly the bulbocavernosus muscle. These two muscles form a figure eight crossing in the midline at the connective tissue plate called the perineum.

It was interesting to note the low incidence of operative interference. This is lower than we have in our own hospital. This may be because we teach routine outlet forceps whenever possible for two reasons: first, following the excellent paper by Aldridge in which the lower incidence of morbidity was reported, we believe it is a good procedure; and second, we are anxious to teach our interns this procedure as an introduction to obstetric surgery.

I was interested also in the low incidence of cesarean sections. We teach that cesarean section is the procedure of choice in placenta previa and placenta abruptio, unless the surgeon in charge feels that a conservative method can be carried through safely. I noted that there were four placenta previa cases and only two were sectioned, the other two delivered spontaneously, and there were no fetal deaths. Therefore, although I may disagree with general principles in the handling of these cases, I certainly must state that Dr. Smith's judgment has been vindicated by the results. Cesarean section in long labor might be worth considering. We do not consider long labor as an indication of cesarean section per se, although, if we found evidence of cephalopelvic disproportion, we feel that cesarean section is better than long tedious labor with injury to the child.

DR. SMITH (Closing).—We do not routinely inspect the cervix after delivery. It is inspected only when there is reason to question its integrity, as following breech extraction, midforceps, when bleeding is too free, etc.

That the operative incidence is too low is a valid criticism. Late in 1946, it began to increase, and stayed higher through 1947. The institution of resident training seemed to correspond with the beginning of the increased operative incidence.

Three factors enter into an explanation of the low cesarean section rate. One is an almost complete freedom from any pressure from husbands, mothers, or other interested parties. The second is a rather conservative view of obstetrics in general. Third, it is a very small series of deliveries. No doubt a larger series will show an increased rate.

Few of the prolonged labors were considered to be trial labors. Cephalopelvic disproportion had been considered earlier in labor and usually had been eliminated as a possible cause of the prolongation.

that one patient had had a sphincter tear ten years prior to the complete tear sustained during the period of this series. Another had had a previous low forceps delivery of a 6 pound 2½ ounce infant with no tear. This time with a normal spontaneous delivery of a 6 pound infant, an incomplete third degree laceration was sustained.

Of every fifteen patients admitted to our antepartum clinic, one is a potential bony-pelvis-dystocia problem. It was noted that of the 159 third degrees 43 cases or 27 per cent of the series had clinical abnormalities of the bony pelvis. Thirty of this group had obvious contraction at the outlet, with a narrow pubic arch. The ratio of bony pelvic contraction of one to fifteen in the antepartum clinic compared to one to 3.5 in this group leaves very little question about consideration of the contracted bony pelvis as an etiological factor. This high percentage of abnormal pelvises as a cause attains more significance if one considers the fact that the trained resident staff delivered 20 of these, while the interns delivered twenty-three.

B. *Fetal Factors*.—The average weight of infants delivered in this series was 7 pounds 1 ounce, or 3,200 grams. It is estimated that the average sized baby delivered at this hospital is 7 pounds 8 ounces, or 3,400 grams.

C. *Labor, Delivery and Operator*.—DeLee points out that prolonged labor causes edema of the perineum, making it more friable. Thirty-one, or 19.5 per cent, of these cases had labor longer than twenty-four hours. This proportion far exceeds the number of prolonged labors in the remainder of the deliveries.

Table II attempts to show the various positions of the fetus as found by the designated authors. Our series showed no position to be excessive. The distribution is such that we find it necessary to discount position as a serious cause of third degree lacerations.

TABLE II. POSITION AS A CAUSE

	OUR SERIES	WILLIAMS ¹⁴	DE LEE ¹⁵
Total	159	6877	35,179
LOA	46 %	54 %	
ROA	28 %	25 %	
LOP	3.1 %	9 %	
ROP	7.5%	12 %	52.7 %
Breech	3.8 %	3.9%	4.2 %
Face	.6%	.6%	.33%

Tables III and IV evaluate the operator and operative procedure. Obviously the greatest percentage of tears occurred in the low forceps deliveries. The resident on obstetrics delivers about half as many as the intern by low forceps. This proportion tallies with the amount of third degree tears each sustained. Although low forceps is an important cause of third degree tears, it seems as though the skill of the operator at the hospital staff level does not prevent this condition.

Of this group 142 had median episiotomies; fourteen had mediolateral, and three patients had none. Obviously median episiotomies are precursors of third degree tears. However, the literature on median episiotomies attempts to justify its use. Phaneuf¹⁶ states that they are easier to repair and if anatomically brought together leave a more elastic perineum. The third degree that develops frequently with this type of perineum can be prevented by continuing the episiotomy to encircle the anus. He points out that rectoeces rarely occur after complete laceration of the perineum. This tends to prove that it is not the perineum that is responsible for this defect, but rather the stretching and relaxation of the fascial structures of the posterior vaginal segments. Barrett¹⁷ emphasizes the fact that lateral episiotomies cause greater deformity and a more difficult

DeLee¹⁰ in describing the pathogenesis of these injuries, believes that the muscle suffers less actual injury than the fascia. It is the destruction of the fascia that allows the muscle bundles to fall into new arrangements, thus changing the point of attachment to the vagina, rectum, and anal sphincter. When the perineal body is torn, the urogenital septum is destroyed. The anterior wall of the vagina sags. The posterior wall rolls out, and the introitus is permanently open. Dwight Van Dell,¹¹ in a discussion of pathogenesis of third degree tears, states that pressure on the perineum and its lack of retraction with its subsequent anemia and tenseness lead to this injury. The levators give and, because of its firm attachment to the sphincter ani, expose the latter to the full force of the fetal mass. In incomplete tears only repair of the urogenital diaphragm and sphincter ani will control the sphincter action of the bowel. These maintain continence under pressure.

The perineum has two functions. It guides the flexing head until the occiput stems under the symphysis. This is followed by its stretching to insure necessary extension. This stage of the delivery has been treated by various methods. Manual dilatation of the perineum has been used for many years. DeLee¹² points out the following in a discussion of this procedure: "Manual dilatation of the perineum led to an intact mucosa but the underlying fascial layers stretched and separated causing the common injury of parting of the two levator pillars as they embrace the rectum; the few Lushka fibers and the inter-columnar fascia being torn resulting in a diastasis similar to that of the rectus abdominis muscles." However, it did fulfill the extension function of the perineum. The procedure next used was episiotomy after flexion of the head. This procedure, along with the Ritgen maneuver, certainly helped to prevent the mechanical forces that go to create relaxed perinea. Episiotomy had therefore obviated the perineum's extension function. With the onset of prophylactic forceps both functions were practically excluded. The perineum previously serving as a barrier subject to the geometry of forces was almost completely disregarded.

Material Studied

Table I illustrates the distribution of third degree lacerations in this series. One hundred fifty-nine or 1.63 per cent of the total deliveries sustained third degree tears. Of these, 59 or 0.62 per cent were complete, and 100 or 1.01 per cent were incomplete. Its occurrence according to gravidity is noted. Waters¹³ reports twelve cases of third degree laceration after median episiotomy of 373 deliveries, an incidence of 3.2 per cent.

TABLE I. INCIDENCE OF THIRD DEGREE LACERATIONS

	DELIVERIES	THIRD LACERATION	COMPLETE	INCOMPLETE
Primigravida	3,022	148 or 4.9 %	54 or 1.7 %	94 or 3.1 %
Multigravida	6,148	11 or .15%	5 or .08%	6 or .09%
Total	9,170	159 or 1.63%	59 or .62%	100 or 1.01%

Etiology

Causative factors are divided into maternal, fetal, labor, delivery, and operative. The etiology has been outlined during these many years of obstetric history. It is our hope to point them out as we found it. In our analysis, some of these causes assume less significance, some more.

A. *Maternal Factors.*—The average age of this group was 22 years. Table I illustrates the fact that third degree laceration is usually a complication of primigravida. The previous obstetric history in the multigravida series revealed

begun at the upper angle runs down the perirectal fascia to the capsule of the sphincter ani. By everting the caught sphincter ani muscle this suture can be used to approximate the posterior fascia of the capsule. The sphincter is then brought together by two mattress or two interrupted catgut sutures. When this is accomplished the anterior layer of the capsule is closed by carrying the fascial suture forward. A routine episiotomy repair then follows.

The postoperative care is simple. It consists of the following:

1. Low residue diet.
2. Mineral oil.
3. Carlsbad Salts or Phoso-Soda drams one as soon as tolerated after delivery, and four times a day after that.
4. Heat lamp to perineum twenty minutes, twice daily.
5. If there has been no bowel movement by the third day: (a) Oil retention enema drams three given with a rubber catheter size 20. (b) Soap suds enema in 4 hours if oil has not been expelled.

Follow-Up

Of the 159 patients, there were 26 who ran a moderately morbid course. The infection above in no way affected wound healing. There was only one perineum that healed poorly. Postpartum observation at six weeks and up to five years on 134 cases revealed healed perineae with no symptoms. One hundred fifteen of these had a notation on their records to the effect that there was good sphincter tone and control. The several cases whose charts evidenced trouble are outlined as follows:

CASE 1.—The perineum was healing poorly at the time she signed out of the hospital. She was never seen again.

CASE 2.—At delivery because of a severely bleeding hemorrhoid, this patient was packed tightly and tissue approximated by hemostatic sutures. A secondary repair was done at a later date.

CASE 3.—The patient reported incontinence of gas during the second pregnancy, but was asymptomatic before and after that delivery.

CASE 4.—The patient had a poor result after the first repair. A secondary operation was done at a later date.

Nineteen of these patients had subsequent deliveries at this hospital. The operator was not aware of the previous history and took only usual delivery precautions. There was no repetition of the third degree laceration. Of these patients, four had median episiotomies. Four had second degree lacerations. One had a right mediolateral episiotomy. The remainder delivered with intact perineae. In contradistinction to secondary repairs of lacerated perineae these patients can deliver from below without recurrence. Barrett²⁰ believes a cesarean section should be performed in order to prevent recurrence. Ernall and Ferteta²¹ in a study of 205 surgical repairs of complete lacerations, state that of 39 subsequent pregnancies, 21 had recurrence of the tear. The operator was unaware of the previous injury and did not guard the perineum at delivery.

Summary and Conclusions

1. One hundred fifty-nine cases of third degree lacerations are presented.
2. A classification of third degree lacerations is recommended for standard use: incomplete if only the sphincter is involved, and complete if in addition the rectum is also entered.
3. Anatomy and physiology of the perineum are discussed and the pathogenesis is suggested.

repair. The thin fibers of the levators retract and are more difficult to approximate. Campbell¹⁸ believes that sometimes extensive mediolateral episiotomies cut the fibers of Lushka that suspend the rectum from the levators. Rectocele later occurs with the stress and strain of defecation and further childbearing. He finds that median episiotomies allow for a repair of the perineal body in a manner that brings the levator ani into their normal position. To him episiotomy exposes lacerations and makes it accessible for primary repair. DeLee repeats the same principle when he says that all episiotomies prevent further tearing and allow visualization of tissue for a proper anatomic repair.

TABLE III. TYPE OF DELIVERY AS A CAUSE

	SPONTANEOUS DELIVERY	LOW FORCEPS	MIDFORCEPS	BREECH
Total	6202	1886	259	362
Series	22	123	8	6
Per cent of total	0.35%	6.5%	3.09%	1.93%

TABLE IV. OPERATOR AS A CAUSE

	INTERN	RESIDENT
Spontaneous delivery	19	3
Low forceps	71	30
Midforceps		8
Low forceps rotation	8	14
Breech		6
Total and per cent	98 or 61.2%	61 or 38.8%

Campbell¹⁸ postulates that at the stage where extension in delivery occurs the perineum has to be relaxed. If intense spasm occurs as is often produced by light anoxic anesthesia, lacerations comparable to direct violence may result. Our series points out that the highest percentage occurred in those who had pudendal block for delivery. Here the uterine contractions and the perineal pressure developed factors that could not be controlled by the operator. General anesthesia gave the best results. Local and regional anesthetics with the patient awake are effective for low forceps deliveries only when all perineal pain is relieved. The pudendal block does not provide this anesthesia while the caudals and spinals do. When a third degree occurs in the latter and general anesthetics, the conduct of delivery may be entirely at fault.

TABLE V. TYPES OF ANESTHESIA AS A CAUSE

ANESTHESIA	TOTAL	NUMBER AND PER CENT OF THIRD DEGREE LACERATIONS
None	5460	14 or .32%
Gas-oxygen-ether	1474	46 or 3.1 %
Gas-oxygen	861	24 or 2.8 %
Pudendal	835	68 or 8.1 %
Caudal	90	3 or 3.3 %
Spinal	77	4 or 5.2 %

Repair and Postoperative Care

The repair and postoperative care at this institution follows the plan suggested by Royston.¹⁹ Chromic catgut 00 or 000 on an atraumatic needle is used. A suture is started at the angle of rectal tear submucosally. This is brought down in this layer to the mucocutaneous junction where it is locked and put aside to be used in the subcuticular stitch for the perineal skin. A second suture

APPENDICITIS OCCURRING DURING PREGNANCY

A Diagnostic Review of 200 Cases

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THE subject of appendicitis as it occurred during pregnancy presented certain findings which, when recognized, may eliminate operation in many cases and save life in the occasional instance.

The material presented here was obtained through the courtesy of four hospitals in Detroit, Mich. Receiving Hospital is a municipal institution that has no obstetric service. Woman's Hospital devotes one-half of its services to obstetrics. Grace and Harper Hospitals are general hospitals and support active obstetrical services.

For the purpose of discussion, this series was divided into the following groups. (Table I.)

TABLE I. GROUPING OF CASES FOR DISCUSSION ACCORDING TO TISSUE DIAGNOSIS

1. Acute (catarrhal, gangrenous, gangrenous with general peritonitis)	52
2. Nonacute	125
3. Interval operation (not discussed)	2
4. Discharged without operation	21
Total	200

The number of cases was inadequate for statistical study; however, certain trends were presented. Table II demonstrated that pregnancy and appendicitis were more common in the early age groups. Table III presented a definite suggestion of seasonal occurrence in the acute cases. The nonacute cases were spread evenly throughout the year. This would be expected if the lower abdominal pain often associated with pregnancy was confused with the pain associated with acute appendicitis. Table IV indicated that the acute cases occur throughout the pregnant state as one would expect if there were no relationship with pregnancy per se. In the last trimester there was only one case in the "nonacute" group.

TABLE II. AGE VERSUS APPENDICITIS AND PREGNANCY

	UNDER 20 YEARS	20 TO 25 YEARS	26 TO 30 YEARS	31 TO 35 YEARS	OVER 35 YEARS	NO RECORD
Acute	5	20	19	5	2	1
Chronic	19	69	32	15	13	0

TABLE III. SEASONAL OCCURRENCE OF ABDOMINAL SYMPTOMS

	JAN.	FEB.	MAR.	APR.	MAY	JUN.	JUL.	AUG.	SEP.	OCT.	NOV.	DEC.	NO REC- ORD
Acute (52)	4	8	2	5	0	3	0	5	8	4	4	7	2
Nonacute (125)	11	8	12	11	11	10	8	12	9	10	12	11	1

4. The use of median episiotomy is recommended and its use justified despite its association with third degree lacerations.

5. Causes of third degree laceration such as contracted outlet, size of fetus, position, anesthesia, forceps are analyzed.

6. A simple repair and postoperative treatment is outlined.

7. The follow-up on this series, though incomplete, is sufficient evidence that all fears may be allayed in the treatment of third degree lacerations. As long as an accurate anatomical repair is performed the results will usually be good.

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only 27 cases. Rebound tenderness, pain in upper right quadrant, Rovsing's sign and psoas sign were the other palpatory signs mentioned. It was apparent that the usual physical signs were poorly demonstrable or absent in about one-half of the cases. The displacement of the appendix by the enlarging uterus does not present the complete answer. (Table VI.)

TABLE VI. PHYSICAL EXAMINATION

ACUTE CASES (52)		NONACUTE CASES (125)	
Muscle spasm	9	Muscle spasm	3
"Spot" pain	27	"Spot" pain	0
Rebound tenderness	8	No record on chart	14
Right upper quadrant pain	1	Mass recorded	10
Rovsing's sign	1	Other signs: Bilateral abdominal pain; lower abdominal pain; distention; rebound tenderness	
Psoas sign	2		

An analysis of the "nonacute" cases revealed that no case presented a history sequence of sudden onset, abdominal cramps, and localization of pain. Four cases presented abdominal pain followed by localization over McBurney's point that could be suspected of acute disease.

The duration of the abdominal pain was of interest. In 44 cases, the duration was not mentioned but was probably short; 48 cases had pain one month or longer; 21 cases had pain one week or more; 12 cases had pain two days or more.

Prominent complaints in order of their frequency are shown in Table V.

Abdominal examination of the "nonacute" cases revealed no instance of finger-tip localization of pain. Slight pain on deep palpation over McBurney's point or the right lower quadrant was mentioned in 49 cases; the absence of pain was recorded 26 times; no record on chart in 14 cases. A mass was noted on the chart in 10 cases. Bilateral abdominal pain, pain in lower abdomen and in the gallbladder region, right rectus spasm, rebound tenderness and distention were mentioned in two or three instances each. (Table VI.)

Blood Counts

The blood pictures were limited to simple blood counts. They were found to be unreliable as diagnostic sides. A group of 51 cases of acute appendicitis had recorded blood counts which ranged from 8,000 to 31,000 total white cells per c.mm. In approximately one-third of these cases, the white cell count was below 14,000 per c.mm. The polymorphonuclear counts ranged from 68 per cent to 95 per cent. In two-thirds of these cases the "poly" count was 80 per cent or less.

There were records of blood counts in 89 cases in the "nonacute" group. In two-thirds of the cases, the total white cell count ranged from 6,000 to 12,000 cells per c.mm. and the polymorphonuclear count was between 60 per cent and 80 per cent. In the remaining one-third, the total count rose as high as 23,000 cells per c.mm. and the differential polymorphonuclear count as high as 95 per cent. (Table VII.)

TABLE VII. BLOOD COUNTS (WHITE AND DIFFERENTIAL)

ACUTE (51)		NONACUTE (89)	
Total counts 8,000 to 31,000		Total counts 6,000 to 23,000	
33 per cent below 14,000		66 per cent 12,000 or below	
Polymorphonuclear 68 per cent to 95 per cent		Polymorphonuclear 60 per cent to 95 per cent	
66 per cent were 80 per cent or less		33 per cent were 80 per cent or more	

TABLE IV. MONTH OF GESTATION VERSUS OPERATION

	1	2	3	4	5	6	7	8	9	NO RECORD
Acute (52)	0	9	12	8	7	6	5	1	3	1
Nonacute (125)	1	48	27	17	6	8	1	0	0	17

Anamnesis

An analysis of the "acute" cases showed that the most important aspect of diagnosis was an accurate history. There was evidence of a sudden onset of symptoms in 41 cases. In the remaining 11 cases, abdominal cramps lasted from one to two days. Generalized abdominal cramps were present in 45 cases. Cramps were present over the right lower quadrant in six cases and over the lower abdomen in one case. There was spot localization of pain in 50 cases and no localization in two cases. In the two cases not complaining of spot pain, there was a positive psoas sign. Additional complaints were found in eight cases. (Table V.)

TABLE V. HISTORY

ACUTE CASES (52)			NONACUTE CASES (125)		
<i>Onset:</i>	Sudden	41	<i>Onset:</i>	Sudden	0
	Prodromal			"Short time"	44
	(1-2 days)	11		2 days \pm	12
				1 week \pm	21
				1 month \pm	48
<i>Cramps:</i>	Generalized	45	<i>Cramps:</i>		0
	Right lower quadrant	6			
	Lower Abdomen	1			
<i>Localization:</i>	"Spot"	50	<i>Localization:</i>	"Spot"	0
	No	2	<i>Prominent</i>	Pain right lower	
	Psoas sign	2	<i>complaints:</i>	quadrant	70
				Abdominal pain	23
				Nausea and vomiting	54
				Vaginal bleeding	8
<i>Other Complaints:</i>	Diarrhea	5	<i>Other</i>	Vaginal discharge;	
	Protracted vomiting	2	<i>complaints:</i>	menstrual pains;	
	Vaginal bleeding	1		malaise; diarrhea;	
				backache; dizziness;	
				dysuria; costo-	
				vertebral pain	

Comment.—The anamnesis of acute appendicitis evolves about a triad of events. First, there is the sudden onset which occasionally may be preceded by a period of vague gastrointestinal symptoms. Secondly, there are crampy pains projected over an area of the abdomen, usually associated with some degree of nausea and/or vomiting, which can be described as the peristaltic phase of the disease. These cramps cease before the third phase is fully developed. The third phase is the localization of a steady, dull pain definable by the tip of the patient's finger and may be termed the phase of peritoneal irritation. This triad indicates the presence of acute appendicitis with few exceptions, regardless of any contrary physical or laboratory findings. In the rare instance, an acutely inflamed low-lying gall bladder or Meckel's diverticulum may give a similar picture.

Abdominal Examination

Physical examination of the patients in the "acute" series revealed an interesting lack of findings. Only 9 cases presented rectus or abdominal wall spasm. The records of 18 cases made a special note that no muscular rigidity was present. Local pain over McBurney's point was present to palpation in

Examination.—Localized pain over McBurney's point.

Laboratory.—White blood cells 11,700, polymorphonuclear leucocytes 78 per cent.
Sent home after three days.

CASE 3.—M 2369, white, 19 years old, primipara, 2 months' gestation.

History.—Generalized abdominal pains of two days' duration associated with nausea, localization of pain in lower right quadrant.

Examination.—Slight pain on palpation over McBurney's point.

Laboratory.—White blood cells 9,450 polymorphonuclear leucocytes 56 per cent.
Discharged.

CASE 4.—M 9809, white, 20 years old, primipara, 4 months' gestation.

History.—Pain over the right lower quadrant associated with vomiting of 4 days' duration, localization of pain over McBurney's point, which was relieved by application of ice to abdomen and aggravated by motion.

Examination.—Pain localized over McBurney's point.

Laboratory.—White blood cells 13,200; polymorphonuclear leucocytes 74 per cent.
No operation.

CASE 5.—106435, white, 24 years old, primipara, at term.

History.—Generalized abdominal cramps (interpreted as pseudo-labor) associated with vomiting, localization of pain in right lower quadrant.

Consultation.—"Suggestive of acute appendicitis or twisted omentum, watch blood counts."

Laboratory.—Counts taken every six hours:

White blood cells	Polymorphonuclears
25,400	89%
17,500	79%
19,600	83%
18,400	86%
16,900	89%
18,300	88%
13,100	83%

Attack subsided; discharged.

CASE 6.—L 10198, Negro, 24 years old, para 1, 6 months' gestation.

History.—"Sore throat" and generalized abdominal pain for one week; marked pain in right lower quadrant associated with polyuria, dysuria, diarrhea of two days' duration.

Examination.—Generally toxic; severe pain in right lower quadrant.

Laboratory.—Hemoglobin 12 Gm.; red blood cells, 3,640,000; white blood cells 31,700; polymorphonuclear leucocytes 93 per cent with "toxic granulation."

Operation.—Spinal anesthesia; drainage of abscess through McBurney incision.
Expired on operating table.

CASE 7.—B 35600, white, 29 years old, para 1.

History.—Epigastric pains; localization in right lower quadrant associated with vomiting, two days' duration.

Examination.—Tenderness right lower quadrant and right upper quadrant.

Laboratory.—White blood cells 11,650; polymorphonuclear leucocytes 90 per cent.

Operation.—McBurney incision; gangrenous appendix removed; abdominal drains inserted; culture negative for growth; died fifth postoperative day.

Autopsy.—Septic emboli in the mesentery; gangrenous bowel.

CASE 8.—58141, white, para 1, at term.

History.—Previous admission 6 days previously, discharged after unsuccessful attempt at induction of labor (quinine, oleum ricini, Pitressin). December 1, onset of generally severe and colicky abdominal pains, followed by nausea and vomiting; localization of pain in right lower quadrant.

Cases Discharged Without Operation

A group of twenty-one cases were admitted to the hospital with a diagnosis of acute appendicitis but were sent home after a period of observation. Five of these cases presented a definite history of active appendicitis; they should have been operated upon promptly, in my opinion. Accurate evaluation of the condition of the appendix by any diagnostic means at our disposal is not reliable in cases of pregnancy. Postponement of operation may be extremely dangerous, while early operation is relatively safe. One of the cases presented here was followed by repeated blood counts, a notoriously inadequate procedure as this paper demonstrates. A brief résumé of the case histories of the challenged cases are as follows. (Case reports Nos. 1, 2, 3, 4, 5.)

"Missed Diagnosis"

A group of fifteen cases presented problems of differential diagnosis as they were encountered in this study. The appendix was removed incidentally after the true diagnosis had been made at operation. Eight cases involved a consideration of ectopic gestation, of which five cases had a preoperative diagnosis of tubal pregnancy which was not confirmed; one case was a hematoma following ruptured ectopic pregnancy that was diagnosed as appendiceal abscess; one case was a true ectopic pregnancy diagnosed as acute appendicitis; one case was a missed abortion diagnosed as ectopic.

There were three cases in which the tumor of pregnancy was diagnosed as an ovarian cyst and two cases were diagnosed as fibroid uteri. One case of acute right lower lobar pneumonia with referred abdominal pain and two cases of acute pyelonephritis were operated upon for acute appendicitis. (Table VIII.)

TABLE VIII. MISSED DIAGNOSIS (15). APPENDIX REMOVED AFTER CORRECT DIAGNOSIS WAS MADE

PREOPERATIVE DIAGNOSIS	POSTOPERATIVE DIAGNOSIS	
(1) Acute ectopic pregnancy	Normal tubes	5
(2) Acute ectopic pregnancy	Acute appendicitis	1
(3) Acute ectopic pregnancy	Missed abortion	1
(4) Acute appendicitis (abscess)	Hematoma	1
(5) Ovarian cyst	Central pregnancy	2
(6) Fibroid uterus	Central pregnancy	2
(7) Acute appendicitis	Acute lobar pneumonia	1
(8) Acute appendicitis	Acute pyelonephritis	2

Mortality

The mortality in the entire group was 2 per cent; in the "acute group" it was 7.7 per cent. It is conceivable that all deaths could have been prevented by the courageous and prompt action of the patient and physician. Early consultation with the abdominal surgeon would seem advantageous. A short résumé of each case is presented. (Cases 6, 7, 8, 9.)

CASE 1.—B 25400, white, 21 years old, primipara.

History.—Abrupt onset of epigastric cramps, continuous vomiting, obstipation, localization of pain in right lower quadrant.

Examination.—Right rectus spasm; deep pain over McBurney's point; temperature 98.2° F.

Laboratory.—White blood cells 11,700; polymorphonuclear leucocytes 78 per cent.

The attack subsided; discharged.

CASE 2.—B 25913, white, 23 years old, primipara, 3½ months' gestation.

History.—Sudden onset of epigastric pains, increased amount of nausea and vomiting, localization of pain over McBurney's point.

CARCINOMA OF THE VULVA

A Review of Fifty Cases

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DURING the ten-year period from January, 1937, through December, 1946, there were 50 cases of proved carcinoma of the vulva admitted to Charity Hospital at New Orleans. This represents 2.4 per cent of all malignancies of the female genital tract (2,058), and 0.11 per cent of all gynecologic admissions (44,770) during this period. Included in this series are all histologically confirmed malignant lesions arising in the labia, clitoris, Bartholin's glands, and vestibule. Also included is one case of periurethral carcinoma.

The youngest patient in the group was 23 years of age and the oldest 80, the average age being 53.4 years. This is somewhat less than the average age of 58 to 60 reported by Taussig,³⁰ Graves and Mezer,⁷ and Folsome.⁶ Twenty-one cases (42 per cent) occurred in patients under the age of 50, but the greatest actual number (10) occurred in the eighth decade (Table I). Sixty-six per cent of the patients had reached or passed the menopause before presenting themselves for diagnosis. Twelve women were nulliparous while 38 had borne one or more children.

Shannon and Marting,²³ in reviewing the literature, cited five cases of carcinoma of the external genitals complicating pregnancy and added a report of a sixth case. Four of these presented carcinoma of the vagina, and two carcinoma of the vulva. Included in this series are two patients, both Negro, in whom the lesions of the vulva were first discovered during pregnancy. One of these patients, aged 29 years, is alive four years following partial vulvectomy and has had one subsequent pregnancy. The other patient, aged 27 years, is alive and apparently well eighteen months after a vulvectomy and bilateral lymph node resection, performed one month following the vaginal delivery of a living child. Thirty-one cases (62 per cent) occurred in Negro women, a total of 0.13 per cent of 24,481 Negro gynecologic admissions during this period. In white patients the incidence was 0.09 per cent of 20,289 admissions. Thus, this series shows no great difference in the incidence of vulvar carcinoma in Negro and white women in the New Orleans area.

TABLE I. AGE INCIDENCE

AGE (YEARS)	NO. OF CASES
20-29	4
30-39	9
40-49	8
50-59	8
60-69	9
70-79	10
80-89	2

It is discouraging to note the time elapsed from the onset of symptoms to the time the patients first sought admission to the hospital (Table II). The shortest period of time elapsed was two weeks, the longest ten years.

Laboratory.—White blood cells, 12,000, polymorphonuclear leucocytes 96 per cent; non-filamented 8 per cent.

December 2, consultant believed condition due to toxemia of pregnancy. December 3, baby delivered stillborn after medical induction. Temperature normal. Nausea, moderate distention. White blood cells 28,000; polymorphonuclear leucocytes 95 per cent; nonfilamented 7 per cent. December 4, marked distention; temperature 100.6° F., diagnosis of acute appendicitis made and medical treatment advised.

Died on tenth day.

CASE 9.—10859, white, 20 years old, primipara, at term, admitted April 24, 1947.

History.—Admitted to hospital with complaint of increasingly severe right costovertebral pain which radiated to right flank.

Examination.—Pain over right costovertebral angle, temperature 99° F.

Laboratory.—Red blood cells 3,160,000; white blood cells 29,800; polymorphonuclear leucocytes 84 per cent; stabs 31 per cent; urinalysis, negative; penicillin given in adequate dosage. April 26, 1947, pain in right costovertebral angle became more severe and radiated to the right flank and the right lower quadrant; vomiting occurred and shortly afterward there was localization of pain in the right lower quadrant.

Examination.—Marked costovertebral pain, slight tenderness in the right flank but no abdominal pain. Catheterized urine specimen revealed an occasional pus cell.

Diagnosis.—Acute pyelonephritis of right kidney concurred in by consultant.

April 27, 1947, severe dyspnea developed; the pain in right costovertebral angle was more severe, a cough developed.

Examination.—Marked abdominal distention, no peristalsis to auscultation. Chest x-ray revealed acute pneumonic process at both bases. The diagnosis became obvious, and conservative treatment was advised, which was carried on energetically.

The patient succumbed on the eighth day. Post-mortem revealed gangrenous appendicitis, generalized peritonitis, pyelonephritis, bilateral lobar pneumonia of lower lobes.

Summary and Conclusion

The anamnesis of acute appendicitis in the pregnant woman was the same as that in any other individual and it was the most reliable feature in the diagnosis.

Physical examination was misleading because the usual findings in over one-half the cases were either poorly demonstrable or absent altogether.

The simple blood pictures were poor diagnostic aids. Many of the acute cases had counts within the upper limits of normal while many of the nonacute cases had counts usually associated with advanced suppurative appendicitis or peritonitis.

The deaths were found in the well-advanced cases of appendicitis and peritonitis.

The most important factor to be considered in the differential diagnosis was the pain associated with the enlarging uterus in the early stage of pregnancy and the "lightening" pains of the mother at term.

If there is a definite anamnesis of appendicitis accompanied by poor or absent physical signs and an inconclusive blood picture, this report strongly suggests that immediate operation is indicated.

TABLE III. POSSIBLE PREDISPOSING FACTORS

Granulomatous venereal lesions	18,
Leucoplakia	9
Papillomatous lesions	4
Trauma	2
Venereal warts	1

TABLE IV. ASSOCIATED VENEREAL INFECTIONS

Syphilis	8
Syphilis and lymphogranuloma inguinale	4
Syphilis, granuloma venereum	1
Syphilis, lymphogranuloma inguinale, chancroid	1
Chancroid and granuloma venereum	1
Chancroid	1
Granuloma venereum	2

All but one of the 21 patients under the age of 50 years were Negro. It is probably significant that 12 (60 per cent) of these Negro patients had one or more of the granulomatous venereal diseases. This evidence suggests that the presence of granulomatous venereal lesions may favor the early appearance of carcinoma of the vulva.

The primary site of the lesion, so far as could be determined was on the labia in 37 cases, in the vestibule in three cases, and in Bartholin's glands in four. In five cases, the initial lesion was on the clitoris. There was an equal distribution between the right and left sides. No attempt was made to separate lesions of the labia into those arising on the labia majora or the labia minora.

Rarely does metastasis to the vulva occur from carcinomas primary elsewhere in the body.⁶ Only one such case was discovered among the 44,770 gynecologic admissions covered in this survey, the patient being a 63-year-old Negro woman who had an adenocarcinoma of the vulva, metastatic from the rectum. This case is not included in the series. Included is one case of malignant melanoma arising in the right labium majus, one case of mixed adenocarcinoma and epidermoid carcinoma apparently arising in the left Bartholin's gland, and one case of extensive Bowen's disease associated with grade III epidermoid carcinoma. One lesion was periurethral in origin and was epidermoid in character. There were three other examples of adenocarcinoma arising in the Bartholin's glands. The remaining 43 lesions were epidermoid carcinomas. Histologic sections were still available for study in 43 of the 50 cases. The seven cases in which the slides were no longer available had been histologically diagnosed by competent pathologists. The 37 cases of epidermoid carcinoma in which slides were available were reviewed and graded. Twenty-three were grade II, 11 were grade III, one was grade IV. Two were unsuitable for grading.

In three patients there was more than one malignancy. All of these patients were white. One woman had a vulvectomy in 1941, at the age of 67 years, for epidermoid carcinoma. She was readmitted in 1944 with a carcinoma of the stomach. At that time the genital lesion was apparently cured. The patient refused surgery and cannot now be traced. The second patient was treated in 1938 at the age of 72 years for epidermoid carcinoma of the hand and nose. In 1940, a malignant melanoma of the vulva appeared and was treated radiologically on the basis of a mistaken diagnosis of epidermoid carcinoma. In 1944, adenocarcinoma of the fundus of the uterus was diag-

In the majority of cases, the presenting symptom was the presence of a "sore" (growth, ulcer) on the external genitals followed in order of frequency by itching, burning, pain, and bleeding. Nine of the patients (18 per cent) had a pre-existing leucoplakia. Other pre-existing lesions included papillomas (type undetermined), in four cases, and venereal warts in one case (Table III). There was a history of mechanical trauma in two cases. Eighteen (36 per cent of the patients) had one or more of the specific venereal infections (Table IV). Syphilis occurred alone eight times, granuloma venereum twice, and chancroid once. Syphilis and lymphogranuloma inguinale occurred together in four cases. There was one case each of the following combined infections: Syphilis and granuloma venereum; syphilis, lymphogranuloma inguinale, and chancroid; chancroid and granuloma venereum. As far as could be determined from the hospital records, none of the white patients in this series had venereal disease.



Fig. 1.—Fungating carcinoma of the vulva in a 27-year-old pregnant Negro woman. Patient was delivered of a living child and one month later a vulvectomy and bilateral lymph node resection were performed. Living and apparently well one and one-half years later.

TABLE II. DELAY IN SEEKING HOSPITAL TREATMENT

DURATION OF SYMPTOMS	NO. OF CASES
Less than 1 month	1
1 to 3 months	9
3 to 6 months	6
6 to 9 months	7
9 to 12 months	1
1 to 2 years	7
2 to 3 years	6
3 to 4 years	3
4 to 5 years	1
Over 5 years	6
Insufficient data	3

lymph node resection was performed, an incidence of 30 per cent. To allow for the conventional five-year follow-up period, those patients treated before January, 1942, will be considered in greater detail (Table VI).

TABLE V. THERAPY, ALL PATIENTS

Vulvectomy with bilateral lymph node resection	10
Vulvectomy with unilateral lymph node resection	1
Hemivulvectomy with bilateral lymph node resection	1
Hemivulvectomy with unilateral lymph node resection	1
Vulvectomy	13
Partial vulvectomy	4
Cautery or excision	3
Irradiation	11
No therapy	6
	<hr/> 50

TABLE VI. THERAPY, 22 PATIENTS TREATED PRIOR TO JANUARY, 1942

MODE OF TREATMENT	NUMBER OF PATIENTS	ALIVE 5 YEARS
Vulvectomy with bilateral lymph node resection	2	2
Vulvectomy	4	1
Partial vulvectomy with unilateral lymph node resection	2	0
Partial vulvectomy	2	0
Excision or cautery	2	0
Irradiation	5	1
No therapy	5	1
	<hr/> 22	<hr/> 5

Twenty-two cases were followed for over five years. Of these, the disease was too far advanced in five to permit any treatment, five received irradiation alone, and twelve were treated surgically. Only two of the twelve patients treated surgically received the complete vulvectomy and bilateral lymph node resection. Both are alive and well after five years. There was microscopic evidence of lymph node metastasis in one of these cases. Two other patients are alive and well after five years. One was treated by simple vulvectomy and the other by irradiation. The latter patient had a malignant melanoma, mistakenly diagnosed as epidermoid carcinoma. Melanoma of the vulva is a rare lesion not ordinarily responsive to radiation but this patient appears to represent an exception to the rule.

A fifth patient had no treatment because of advanced age and general debility, yet she did not die until five years after the diagnosis of carcinoma of the vulva had been made. There was one operative death following vulvectomy. Eight other patients could not be traced and for statistical purposes are considered as dead. Thus the five-year known survival rate is 22.7 per cent and the five-year known cure rate is 18.1 per cent.

The results of irradiation therapy have been unsatisfactory. Healy¹¹ notes that carcinoma of the vulva is seldom seen except in women with some pre-existing vulvar lesion or abnormality. He further states that not even a normal vulva will tolerate the dosage of radiation necessary to destroy a large carcinoma. Extensive ulceration and slough often results from heavy irradiation. Plate,²⁰ at the University of Amsterdam, treated 14 malignancies of the vulva radiologically with no five-year survivals. The patient in this series who were treated by radiation alone were considered inoperable and the treatment was palliative.

nosed and treated radiologically. This patient was still alive in December of 1946. The third patient, aged 55 years, is perhaps the most interesting. In 1930, a radical mastectomy was done for adenocarcinoma of the left breast. In 1934, a papillary adenocarcinoma of the right ovary was removed. Carcinoma appeared in the right breast in 1936 and a second radical mastectomy was performed. Epidermoid carcinoma of the left labium developed in 1940. The patient died two years later. An autopsy was not performed. In none of these cases was there any obvious relationship between the vulvar lesion and the malignancy elsewhere. Although the number of cases is not sufficient for statistical treatment, the presence of three patients with multiple carcinoma in a group of 50 is of interest.

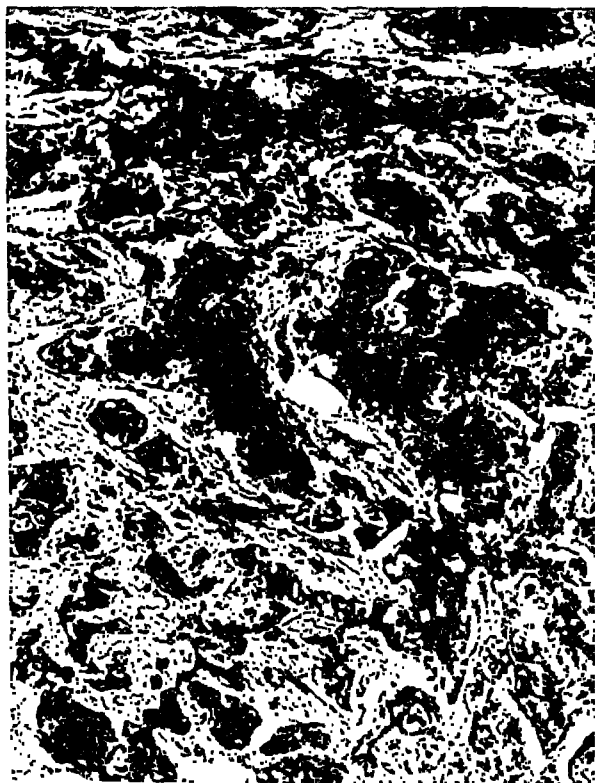


Fig. 2.



Fig. 3.

Fig. 2.—Photomicrograph of epidermoid carcinoma of the vulva showing "pearl" formation.
Fig. 3.—Photomicrograph of adenocarcinoma of the vulva arising from Bartholin's gland.

Autopsies were performed on two patients in this series and in neither was any distant metastasis evident. Eichenberg⁵ autopsied 41 cases of carcinoma of the vulva and found extension as far as the peri-aortic lymph nodes in only five. Distant metastasis, when present, usually occurs late in the course of the disease. The usual spread, even from a unilateral primary lesion, is to the lymph nodes in the groin on one or both sides. Later on, invasion of the deep femoral and obturator nodes may occur. Vulvectomy and resection of the superficial and deep lymph nodes on both sides are therefore indicated.

Thirty-three of the 50 cases comprising this series were treated surgically. Table V outlines the methods of treatment used on all patients in the series. Lymph node metastases were found in four of the thirteen cases in which

AN EVALUATION OF THE GUTERMAN PREGNANCY TEST*

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BETWEEN the years 1903 and 1934 various investigators postulated the corpus luteum to be a gland of internal secretion; carried out experiments to prove this; isolated its hormone (progesterone) and determined its structural formula. In 1929, Marrian¹¹ isolated pregnandiol from the urine of the pregnant woman.

In 1936 Odell and Marrian² showed that most of the pregnandiol recovered from urine exists in a combined form, from which it can be freed by acid hydrolysis. Venning and Browne³ extracted sodium pregnandiol glucuronidate from urine. A quantitative method of assaying urine for sodium pregnandiol glucuronidate was presented by Venning in 1937.⁴ Since 1937 considerable work has been done to prove that pregnandiol, as sodium pregnandiol glucuronidate, represents the excretory product of progesterone metabolism. Weil⁵ demonstrated that hydrolysis of some of the combined form of pregnandiol to the free form occurs spontaneously. He devised a method⁶ for recovering free pregnandiol from urine. Since then, several methods⁷⁻¹¹ have been advanced for assaying urine for both the free and combined forms, either independently or simultaneously.

In 1944 Guterman¹² presented a modification of earlier techniques, particularly that of Astwood and Jones.⁷ He demonstrated the value of pregnandiol determinations in the diagnosis of early pregnancy.^{12, 13} This postulation had been suggested previously by others. The rapidity and inexpensiveness of Guterman's method made it a practical procedure. An accuracy of 92 per cent was reported by Guterman with this method. The presence of 0.4 mg. or more of pregnandiol in 100 c.c. of a first voided morning urine specimen in a woman who has missed an expected menses indicates a normal pregnancy. Attempts to corroborate Guterman's findings have resulted in conflicting reports.¹⁴⁻¹⁶ Critical analysis indicates that the workers who found the method invalid, in some instances at least, failed to adhere strictly to the technique as originally described by Guterman.

This paper represents an evaluation of the Guterman pregnancy test (as based on a color reaction of pregnandiol in the urine) in eighty-six consecutive patients with missed menses in whom there were no symptoms of threatened miscarriage.

Method

For emphasis, the method will be described in detail, including its adaptation to a quantitative technique, using the Klett-Summerson photoelectric colorimeter.¹⁷ Only one departure from the procedure as outlined by Guterman was made. Twelve-hour summaries, rather than the first voided morning specimen, were used.

Collection.—Patients were asked to collect urine specimens as follows: The patient voided at some convenient time, e.g., 8 P.M., and discarded the

*Aided by a grant from the Noshim Rachmomieth Society of St. Louis.

Summary and Conclusions

Carcinoma of the vulva occurs most often in elderly women but may also be seen in younger age groups. Forty-two per cent of the 50 cases in this series occurred in patients under the age of 50, the average age being 53 years. In 2 patients, the disease of the vulva was complicated by pregnancy. In the New Orleans area the disease is as common in colored women as it is in white women. Fifty-eight per cent of the colored women had granulomatous venereal lesions of the vulva. All lesions of the vulva that fail to respond to treatment in a reasonable time should be biopsied, and it is to be emphasized that one negative biopsy does not rule out malignancy. Treatment is surgical and should consist of complete vulvectomy with bilateral lymph node resection. Radiation has some value in palliation but will seldom effect a cure. In a group of twenty-two patients treated prior to 1942 by a variety of methods, four (18.1 per cent) were living without evidence of disease five years later.

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4. The alcohol filtrate (D-3) is evaporated to dryness from the receiving flask over an electric hot plate (in the hood).

E. Color Development and Quantitative Measurement:

1. 10 ml. concentrated sulfuric acid are added to the residue (D-4).

2. Color is allowed to develop for one hour.

3. Aliquots of the solution E-2 are diluted up to a final volume of 5 ml. with concentrated sulfuric acid in a dry Klett curvette tube and the solution thoroughly mixed.

4. The color is read on a Klett-Summerson photoelectric colorimeter, using the blue No. 42 filter.

5. The amount of pregnandiol represented by the absorption reading is obtained from the standardization curve.* Calculations for the dilutions involved are made to ascertain the pregnandiol present in the original sample.

Results

Pregnandiol values of 3 mg. or more for the total twelve-hour summary were considered positive for pregnancy. The following follow-up studies were done to determine the validity of the results. A negative result was considered correct if a normal menses ensued or if passage of time failed to reveal an enlarging uterus. A positive result was considered correct if the passage of time revealed a continuing pregnancy or if an abortion followed at some subsequent period.

Correct correlation between the laboratory procedure and clinical findings was obtained in 96.5 per cent of all cases.

The results are summarized in Tables I and II.

TABLE I

ANSWER	CORRECT	FALSE	PER CENT CORRECT
Positive	58	3	95
Negative	25	0	100
Total	83	3	96.5

TABLE II

CLINICAL STATE	CORRECT	FALSE	PER CENT CORRECT
Pregnancy	58	0	100
Delayed menses	25	3	89.3

Discussion

The use of twelve-hour summaries rather than single voided specimens was instituted due to our inability to obtain consistent results with the latter during our preliminary work with the method. Guterman considers a deep yellow color reaction as his minimum positive, assuming that such a color (equivalent to 0.4 mg. per 100 c.c.) indicates a 24-hour excretion of pregnandiol of 6 to 8 mg. In our experience, such an assumption led to a large number of errors. Studies of others¹⁸ and in our own laboratory indicate that pregnandiol excretion is relatively constant per given period of time and is relatively independent of urinary volume. Calculations of 24-hour output based on the pregnandiol content of a 100 c.c. sample of urine representing

*Standardization curve prepared from pregnandiol supplied by Ayerst, McKenna and Harrison, Ltd.

specimen. From then on all urine voided was saved and collected in a single jar. Twelve hours later (8 A.M.) the patient again voided and added the specimen to the total. The entire volume was then brought to the laboratory, usually that same morning. No preservative or refrigeration was used. The patients were instructed to keep the urine in a cool place during the period of collection. This overnight collection period was selected because it resulted in remarkably little inconvenience to the patient.

Technique.—Determinations were made on the same day, or the following morning, that the specimens were received. The entire volume was measured. The pregnandiol content of a 100 c.c. aliquot was determined. From this determination, the amount of pregnandiol excreted per twelve hours was calculated.

A. Hydrolysis and Extraction of Pregnandiol:

1. One hundred ml. urine, 50 ml. toluene, 10 ml. concentrated hydrochloric acid, and 2 glass beads are added to a 500 ml. flat-bottomed Florence flask.
2. The flask is connected via a one-holed cork stopper to a Liebig condenser (water-cooled, 400 to 500 mm. jacket length) in vertical position and the mixture is boiled vigorously over an electric hot plate for 15 minutes.
3. The flask and its contents are brought to room temperature by cooling under the water tap.
4. The mixture is transferred to a 500 ml. separatory funnel and the lower layer (urine) is drawn off.
5. The toluene layer and emulsion are washed twice with 15 ml. portions of 0.1N sodium hydroxide and then twice with 15 ml. portions of distilled water.

B. Precipitation of Impurities:

1. The washed toluene and emulsion (A-5) are transferred to a 125 ml. Erlenmeyer flask with 2 glass beads.
2. The mixture is boiled over an electric hot plate (in the hood).
3. When the water has evaporated and the toluene mixture is boiling smoothly, 10 ml. of 2 per cent sodium hydroxide in absolute methanol are added.
4. The mixture is evaporated until a granular precipitate appears and approximately one-half of the original toluene volume is reached.
5. The toluene mixture is then filtered, while hot, through a fritted glass filter (medium porosity, Pyrex) with mild suction. (If the filtrate has an orange, pink, or brown tinge, steps B-3, B-4, B-5 must be repeated until the filtrate is yellow or yellow-green.)
6. The precipitate (B-5) is washed with 15 ml. hot toluene.
7. The combined filtrates (B-5 and B-6) are then evaporated to dryness over the hot plate (in the hood), a gentle air stream being used to drive off the last traces of toluene. This avoids charring of the residue.

C. Precipitation of Pregnandiol:

1. Five ml. acetone are added to the residue (B-7) and the mixture is warmed over a hot plate until solution is complete.
2. Twenty ml. 0.1N sodium hydroxide are added slowly and the mixture is boiled for 3 minutes on the hot plate.
3. The flask is then placed in a refrigerator (5° C.) for one hour.

D. Isolation of Pregnandiol:

1. The mixture (C-3) is filtered through a fritted glass filter (medium porosity, Pyrex) with mild suction.
2. The precipitate (D-1) is washed with 15 ml. distilled water.
3. The receiving flask is changed and 10 ml. hot absolute alcohol are passed through the fritted glass filter to dissolve the precipitate.

DETECTION OF EARLY CARCINOMA OF THE CERVIX; THE CONING BIOPSY

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A SIGNIFICANT advance in the problem of uterine cancer has been made in the past decade by investigators who have demonstrated the importance of constant, even fanatical devotion to the clinical and pathological search for early lesions. This concept has altered our approach to these diseases vastly, so that we can properly hope that future therapeutic advances will rest on a firmly established pattern of early diagnosis. The attainment of this objective of early diagnosis could almost content us with our present methods of treatment, for they might suffice to eliminate death from uterine cancer.

Every cervical lesion which raises any suspicion of neoplasm should be biopsied. It has been clearly demonstrated in several gynecological clinics (TeLinde,¹ Johns Hopkins; Younge,² Free Hospital for Women, Brookline) that one can constantly increase the number of early and preclinical lesions discovered, by enthusiasm for biopsy. It has also been observed by several investigators (Pund et al.³ and others) that routine serial or multiple sectioning of apparently normal cervixes removed at hysterectomy for benign uterine lesions will uncover a striking percentage of nonclinical intraepithelial cancers. One can only utilize these facts by more widespread employment of biopsy.

Various punch biopsy instruments are available for obtaining fragments of cervical tissue. These are most successfully used on the friable well-defined cervical lesion. One should take multiple biopsies whenever possible on any suspicious lesion and also on clinically benign erosions which require treatment.

Coning biopsy of the entire squamous-columnar junction must be done at present with the scalpel; this properly requires brief hospitalization for anesthesia but it is rewarded by more accurate information than that obtained by single biopsy; it enables the pathologist to make a complete survey of early lesions and thus furnishes the clinician with the precise data required for proper treatment. This method has become increasingly important as more intraepithelial cancers are detected on single biopsy and one must ascertain whether this represents the intraepithelial edge of an invasive tumor, or an actual preinvasive neoplastic change.

The successful use of the vaginal smear in the detection of early cervical cancer has also forced a revision in our thinking about cervical biopsy for we are frequently presented with a suspicious or frankly positive smear from a

the urinary excretion of an undetermined length of time are therefore often erroneous. The 12-hour summary was used because it inconvenienced the patient only slightly and for practical purposes is as reliable as longer summations.

Cases studied represented individuals who had missed an expected menses and in whom a diagnosis of pregnancy had not been established. This group of patients consisted of private and clinic patients between the ages of 17 and 48 years, primiparas and multiparas. The period of delayed menses varied from one day to 84 days, one-third of the cases being less than fourteen days delayed. Both house and outpatients were included.

In three instances, patients who were being studied as sterility problems revealed pregnandiol curves indicative of pregnancy even before the patient had reported the missed period. This is consistent with the physiology of corpus luteum formation and retrogression and its measurable component, pregnandiol determination.

It is to be noted that the false results in this series were all false positives. Readings higher than are reported in the literature were occasionally obtained. This would indicate that the final product isolated by the procedure may, at times, contain chromogenic material other than pregnandiol. We feel that it may be possible to reduce the amount of such chromogenic contaminant without complicating the procedure or losing significant amounts of pregnandiol.

Summary and Conclusions

1. The Guterman pregnandiol test for pregnancy, modified only in that twelve-hour summaries were employed rather than single voided specimens, was performed in 86 consecutive cases of suspected pregnancy uncomplicated by any symptoms of threatened abortion.

2. An over-all correct percentage of 96.5 per cent was obtained.

3. Guterman's claim that the method represents an accurate and rapid test for the diagnosis of early pregnancy is corroborated.

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patient whose cervix is a clinically normal one or one which harbors a symmetrical, innocent-appearing erosion. Coning biopsy is the only logical technique for securing adequate tissue for study in such cases.

The increasing need for such a biopsy technique which could be performed simply, as an outpatient method without anesthesia has encouraged our search for an instrument to perform this job. Failing to find one, we have designed an endocervical coning biopsy curette* which has satisfied our requirements in preliminary trials.

Fig. 1 illustrates several such coning biopsy curettes of graduated sizes. A width should be chosen to fit quite snugly into the canal for several centimeters. We prefer to steady the cervix with a tenaculum on the anterior lip. With the curette in "open" position, a twisting motion of slight withdrawal will enable the distal cutting cup edge to gain a purchase into the tissue. The proximal cutting cup may then be brought forward to meet the distal one by a fairly rapid, slightly rotating motion which will remove a superficial cone of tissue from the squamous-columnar junction. If the instrument does not fit the canal well, it may be necessary to angulate it slightly in several directions and close the biopsy cups in each position before a complete cone of tissue will be removed. This shift of position may also be valuable in cases of cervical erosion where the squamous-columnar junction is outside the external os.

Fig. 2 is a routine section of a coning biopsy obtained with this curette. It is a surface biopsy of the external os area which has been surgically "conized" in the above-described manner.

Figs. 3 and 4 illustrate further the focal ability of this type of biopsy. This tissue was obtained from the squamous-columnar junction of a patient admitted to the hospital because of intermenstrual spotting. Pelvic examination revealed no area on the cervix suspicious of cancer. A vaginal smear and endocervical coning biopsy were taken on the ward before operation. The following day a dilatation and curettage, and a scalpel biopsy of the cervix were performed under anesthesia. The tissue removed by these conventional techniques was negative; it contained no suggestion of malignancy. However, the vaginal smear was positive, and the coning biopsy confirmed this preliminary detection for it presented incontrovertible evidence of intraepithelial carcinoma of the cervix. The advantage of such a technique which could obtain a sample of tissue from this crucial region of the cervix was clearly demonstrated.

The limitations of such an instrument are evident. One should utilize curettage and scalpel biopsy under anesthesia whenever necessary to supplement the documentation of cases whose diagnosis is not clear. However, this endocervical biopsy curette may be generally used in the clinic or office to secure tissue from the suspicious area of any cervix in simple fashion. It can serve as a useful corollary to the vaginal smear technique in early detection and it could make such detection studies available to pathological laboratories that are not set up for cytological diagnosis.

This renewed emphasis on the detection of early carcinoma of the cervix also demands a fresh approach to classification and treatment. A precise clinical classification of these lesions should help clarify decisions concerning

*This work has been carried forward with the generous cooperation of the Sklar Surgical Instrument Company.

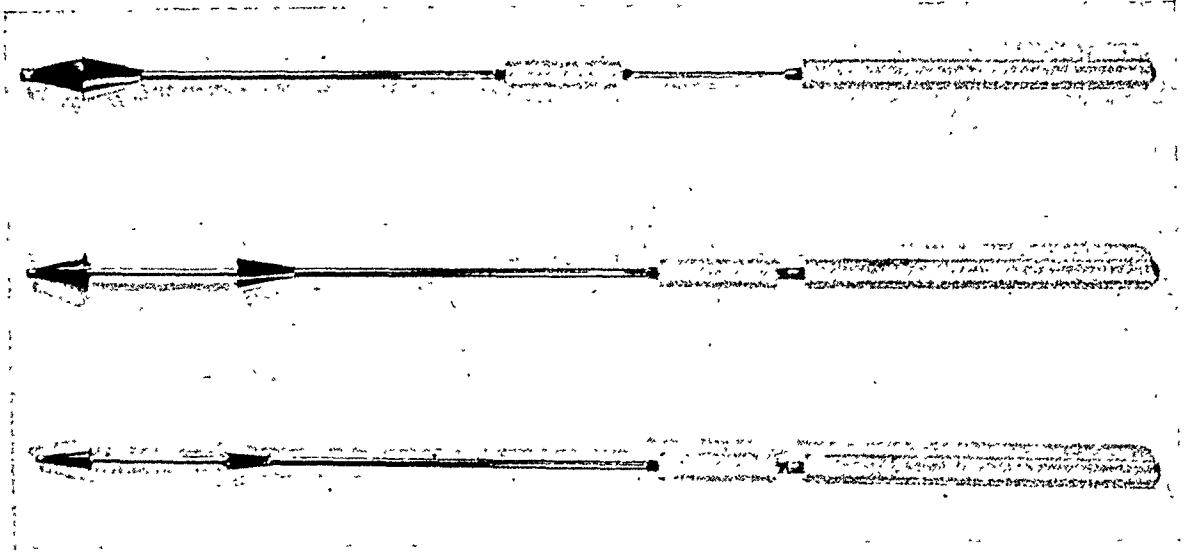


Fig. 1.—Endocervical coning biopsy curettes. The smaller ones are in "open" position, the largest is closed.

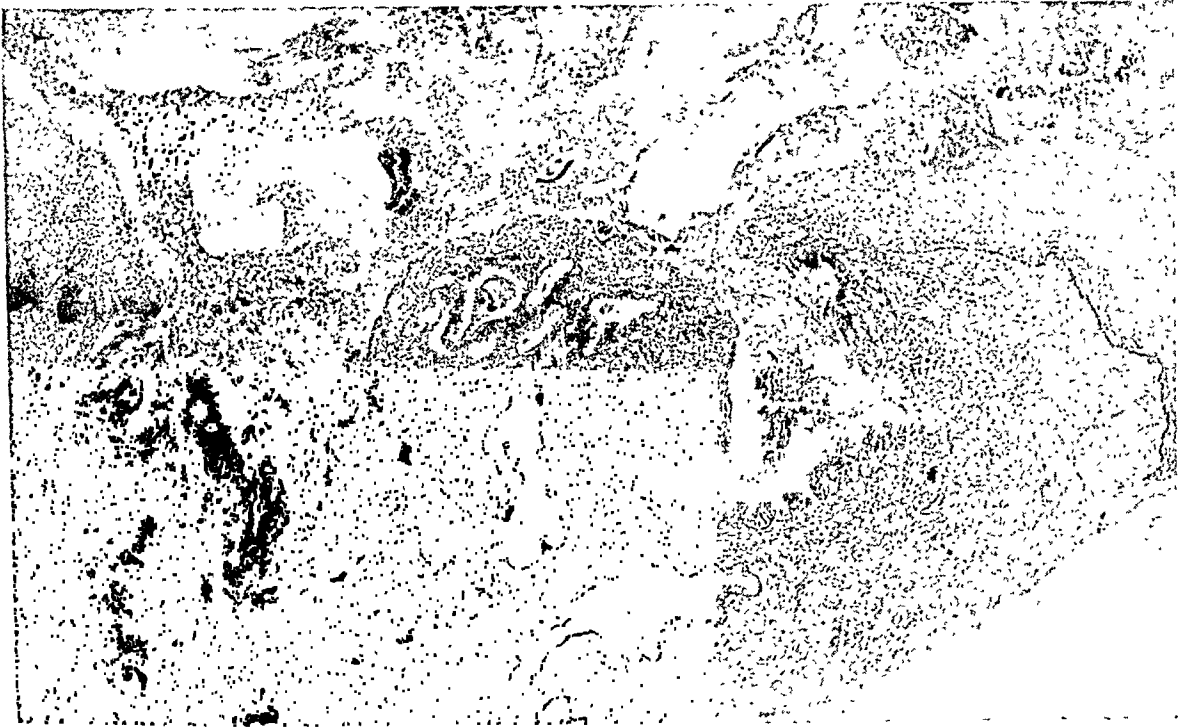


Fig. 2.—Section of endocervical coning biopsy showing a representative sampling of the squamous-columnar junction region. (X70)

treatment and enable investigators to codify their contributions to this important subject with greater benefit to the advancement of our knowledge. A plan which we have used at the Sloane Hospital is herewith presented:

Carcinoma of Cervix

*League of Nations Clinical Classification
Used at the Sloane Hospital for Women* 6*

Stage 0	Intraepithelial carcinoma
Stage I	Lesion confined to cervix
	(A) Cytological (nonclinical lesion, early invasive)
	(B) Small clinical lesion (under 1 cm.)
	(C) Large clinical lesion (over 1 cm.)
Stage II	Usual league of Nations designation
Stage III	Usual league of Nations designation
Stage IV	Usual league of Nations designation

Summary and Conclusions

1. The importance of early detection of cervical carcinoma by frequent biopsy is re-emphasized.

2. A new instrument for obtaining an adequate biopsy in simple fashion is described. This endocervical biopsy curette will secure a general sample of the squamous-columnar junction area.

3. A subdivision of the League of Nations Classification of carcinoma of the cervix which has been found useful in our clinic is presented.

Addendum

Since the preparation of this presentation, another paper (Ayre⁵) has appeared which emphasizes the importance of the coning biopsy and describes a scalpel method of obtaining it.

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*In the Tumor Clinic under the direction of Dr. J. A. Corscaden.

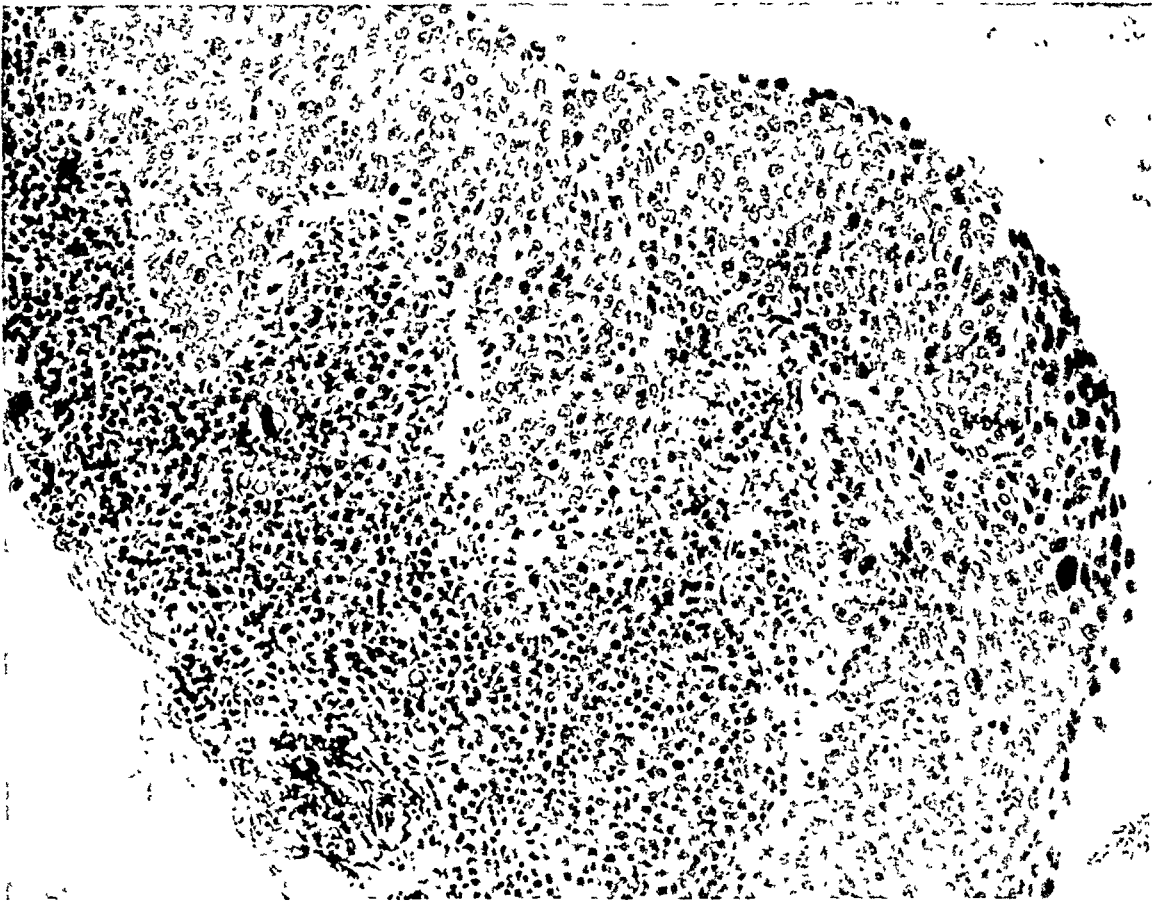


Fig. 3.—Section of endocervical biopsy showing strip of intraepithelial carcinoma. Marked inflammatory reaction is present in stroma. (X150)

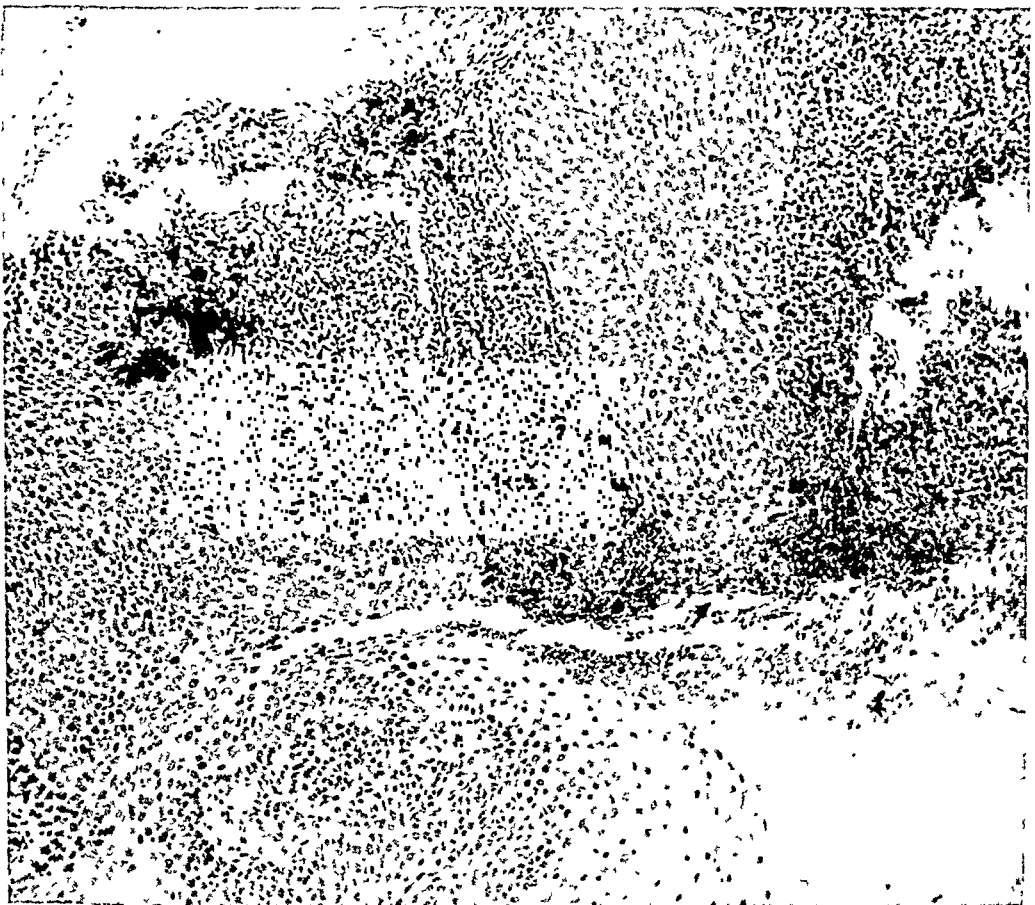


Fig. 4.—Section of endocervical biopsy showing junction of normal and neoplastic tissue. Marked inflammatory reaction is present in stroma. (X125)

Associated with spina bifida and prolapsus uteri in the newborn are numerous congenital defects such as hydrocephalus, scoliosis, kyphosis, clubfoot, infantile uterus, flat and shallow vagina, elongated cervix, and paresis of the perineal muscles, and disturbed sensation in the lower extremities. Neurologic symptoms may be sensory, motor, and trophic disturbances. In a person with clubfoot it is estimated that spina bifida occulta is present in 60 per cent of cases.

Visceral symptoms may be anorectal signs—relaxed sphincter ani, paralysis of the levator ani muscles, rectal and urinary incontinence. Eneuresis is regarded as a prominent symptom.

The diagnosis of occult spina bifida is made definite by x-ray examination. According to the literature there is a wide variation in the incidence of occult spina bifida. Laws⁴ estimates that 4 per cent of all women have occult spina bifida. Ebeler found in 28 cases without prolapse there were only three in which spina bifida occulta did exist. In 28 cases with prolapse, 25 of the 28 showed spina bifida occulta.

Since 1938 one member of our staff has been interested in this observation, and has had x-ray examinations made of the lumbosacral region in his nulliparous patients with prolapse—a total of six cases. Two of these cases, or 33.3 per cent, had occult spina bifida. Two cases showed lumbar scoliosis with convexity to the left and no evidence of occult spina bifida. One case was normal, and the sixth case showed hypertrophic arthritic changes involving the lumbar spine and the right lumbosacral junction. Three additional cases have subsequently been x-rayed and were negative for presence of spina bifida occulta. The total incidence of this series thus is 22.2 per cent.

The above two cases with occult spina bifida present on x-ray study are reported in more detail.

CASE 1.—Aged 58 years, single, was admitted to the hospital on May 1, 1938, with the complaint of burning and frequency of urination, generalized abdominal pain, and a mass protruding from the vagina of one month duration. Physical examination showed the presence of a third degree prolapse of the uterus, relaxed perineum, and generalized abdominal tenderness. There were no cystocele or rectocele present. An x-ray of the lumbosacral region showed the presence of spina bifida occulta of the first, fourth, and fifth sacral segments with hypertrophic arthritis involving the articular facets of the lumbosacral region. Treatment of the prolapse was surgical. A vaginal hysterectomy and modified colpectomy and perineorrhaphy were performed. The patient was discharged on June 2, 1938, in good condition.

CASE 2.—Aged 50 years, single, was admitted to the hospital on Jan. 2, 1944, with the chief complaint of vaginal bleeding and protrusion of a mass from the vagina of several years' duration. Physical examination showed a polyp protruding from the cervix, and a second degree prolapse of the uterus with a moderate sized cystocele and relaxed perineum present. X-ray study of the lumbosacral region showed a lack of osseous union between the lamina and spinous process on the left—first sacral segment, no spinous processes of the distal four sacral segments with lack of union in the neural arches posteriorly. . Diagnosis was spina bifida of the first sacral segment. and spina bifida occulta of the second, third, fourth, and fifth sacral segments. Treatment of the prolapse was a dilatation and curettage, removal of the cervical polyp, Manchester colporrhaphy with amputation of the cervix, and a colpoperineorrhaphy. Recovery was uneventful, and the patient was discharged from the hospital on Jan. 20, 1944, in good condition.

Report of Cases

The following is a report of 19 cases of prolapse of the uterus occurring in nulliparous women, including the two cases reported above. There was a fairly equal distribution of

PROLAPSUS UTERI IN NULLIPARA*

With Reference to the Etiological Role of Occult Spina Bifida

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THE etiological factors in prolapse of the uterus usually have their origin in the stresses incident to childbearing. However, in 963 cases of prolapse of the uterus seen in the Elizabeth Steel Magee Hospital and the St. Francis Hospital in Pittsburgh, Pa., from January, 1934, to April, 1947, there have been 19 cases in nulliparous patients, an incidence of 1.97 per cent.

Predisposing factors in prolapse of the uterus in nulliparas are varied. The uterus is often either congenitally retroflexed or retroverted, and the uterine position is thus in the axis of the vagina and prolapse may ensue either by subsequent trauma as a factor, poor nutrition, intra-abdominal pressure, and/or faulty innervation. Petchenko⁵ reported that nutrition seems to be a factor as the incidence of genital prolapses increased sharply during the German blockade of Leningrad. Secondly, there is also an element of infantilism in many cases of procidentia in nulliparous women. The fact that they are sterile is highly suggestive.

Occult Spina Bifida

Findley³ in 1917 reported two cases of prolapse in nulliparous women, and called attention to the probable relationship of occult spina bifida to this condition. He emphasizes that the pelvic supporting structures, pelvic floor and muscles were relaxed and atrophied.

Spina bifida occulta is defined as a malformation in the laminae of one or more vertebrae, without protrusion of spinal membranes. Willis,¹⁰ after a study of a series of 1,400 skeletons, concluded that anomalies of the spine are confined particularly to the lumbosacral area of the column, and occur as the result of evolutionary, developmental, or environmental influences.

It has been demonstrated at operation or autopsy that together with the bony malformation present, there are, in practically all cases, bands of fibrous tissue extending between the ventral surfaces of the laminae and the dura or the nerve roots, and masses of fat tissue in contact with the nerve roots. The pudendal nerve is the principal nerve for the supply of the perineum. It arises in the pelvis usually by three roots from the second, third, and fourth sacral segments.

The spine grows faster than the cauda equina, and symptoms due to the stretching of the roots may not appear until adolescent or adult life. Trauma may aggravate latent symptoms.

Signs and symptoms of spina bifida occulta may be hypertrichosis, estimated in 4 per cent of the cases, striae, scars, fovea sacralis, and naevi. The local signs are usually absent, and may occur even without occult spina bifida. A subcutaneous lipoma or hemangioma may be present.

*Presented, by invitation, at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Feb. 2, 1948.

5. Treatment is surgical and essentially the same as in multiparas. Results are equally as good. The Manchester type of vaginal repair with or without amputation of the cervix and perineorrhaphy was the treatment of choice. Vaginal hysterectomy has also been done for the treatment of complete prolapse. Some degree of narrowing of the vagina or colpectomy may be done with these operations.

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married and unmarried women in the series—eight being single and eleven married. The age range was from 28 years to 74 years, with an average of 55.3 years.

The prominent symptoms were frequency and burning on urination, protrusion of a mass from the vagina, moderate low abdominal discomfort, backache, tiredness, and some cases had slight to moderate vaginal bleeding. Duration of symptoms ranged from three weeks to twenty-three years.

Essential physical findings were as follows: six patients had first degree prolapse of the uterus, three patients had second degree prolapse, and seven had third degree prolapse. There were three cases showing elongation of the cervix alone, and six cases of elongation of the cervix were present associated with prolapse of the uterus. Moderate to large cystocele and rectocele were present in seven patients, rectocele alone associated with the prolapse appeared in two patients, and cystocele in two patients. Eight patients showed no cystocele or rectocele present, but three of these patients showed a relaxation of the perineum, and one patient a large enterocele.

The surgical treatment of prolapsus uteri in nulliparas is quite the same as in multiparas, and the results seem to be equally as good. All of our cases came to operation. The Manchester type of vaginal repair with perineorrhaphy was performed in ten cases, vaginal hysterectomy was done in four cases, and two cases were corrected by the abdominal approach, one with a vaginal amputation of the cervix and subtotal abdominal hysterectomy, the other corrected by a vaginal amputation of the cervix and an abdominal Coffey suspension of the uterus with no repair of the vagina performed. Three cases had a Sturmdorf amputation of the cervix and posterior colporrhaphy performed. A Watkins interposition operation was done in three cases associated with the Manchester type of repair.

Postoperative examination of thirteen of these cases, or 68.4 per cent of the series, has been made, and there has been no recurrence of prolapse, cystocele, rectocele, or urinary complaints, and the anatomic results have been good.

Summary

1. Nineteen cases of uterine prolapse in nulliparas are reported out of a total of 963 cases of prolapse of the uterus treated in the Elizabeth Steel Magee Hospital and the St. Francis Hospital, Pittsburgh, Pa., covering a period from January, 1934, to April, 1947.

2. Prolapsus uteri in nulliparas is an uncommon yet definite entity, and the series reported shows an incidence of 1.97 per cent. Associated with the prolapse is a relaxation of the pelvic supporting structures. Predisposing factors vary, and there seems to be an indication that neural disturbances with secondary muscular insufficiency of the pelvic floor, atrophy of the ligaments, connective tissue, and muscles contribute to the appearance of uterine prolapse in nullipara. One predisposition to prolapse is congenital, and in these cases where a congenital retroflexion or retroversion exists, subsequent trauma, poor nutrition in early life, faulty innervation, or intra-abdominal pressure may be the exciting cause. There is an element of infantilism in many cases, and the fact that these women are sterile is highly suggestive.

3. Spina bifida occulta should be considered as a possible predisposing factor in uterine prolapse appearing in a nulliparous woman. Nine cases were x-rayed for the presence of occult spina bifida and this condition was found in two cases, or 22.2 per cent. The percentage in this small series is lower than previously reported by others.

4. The presence of cystocele, rectocele, frequency and burning on urination, and relaxed perineum are commonly associated with uterine prolapse.

The patient was 26 years of age at the time of her first pregnancy in 1942. Her past history revealed no illness except the ordinary childhood diseases. Physical examination and Wassermann were negative. The husband had a deformity of one leg as a result of poliomyelitis, but otherwise history and physical examination revealed nothing abnormal. X-rays of the entire spine of both parents revealed no occult spina bifida or other abnormality except for a slight scoliosis of the lower dorsal spine of the husband. Both parents were Rh positive.

The first pregnancy was uneventful and labor began spontaneously at term. An abnormality of the fetal head was suspected during labor. Delivery was accomplished by low forceps. The baby was a girl weighing 3,800 Gm. Gross spina bifida and hydrocephalus were present clinically. About one hour after birth the infant died.

At autopsy the infant had a mongoloid appearance. A defect consisting of absence of the posterior processes of the vertebral column from T-10 to the sacrum was observed. Superficially this defect appeared on a soft area 8.5 cm. long and 5 cm. wide in greatest dimensions. The surface had a red, gelatinoid, raw appearance with only partial epithelialization of the margins. The head was deformed with a greatly increased occipito-mental diameter, and the anterior fontanelle was approximately three times larger than normal. The brain weighed 450 Gm. There was a tremendous dilatation of the ventricular system with numerous hemorrhages of the ependymal surface. Microscopically, pressure atrophy and focal hemorrhages of the cerebral hemispheres were evident.

Major Anatomic Diagnoses.—Congenital hydrocephalus; spina bifida (posterior rachischisis, T-10 to S-1) with hydromyelocele.

After five months the patient became pregnant again but spontaneously aborted at two and one-half months. The fetus was not examined.

In 1943 the third pregnancy occurred. There had been no illnesses during the intervening period. The basal metabolic rate was minus 11 per cent. Because of this, together with occasional spotting in the first trimester, small doses of thyroid were prescribed. The patient fell into labor spontaneously at term. The baby presented by the breech, and was so delivered. The birth weight was 3,100 Gm. The following defects were noted: lumbar spina bifida, hydrocephalus, bilateral equina valgus, flaccid paralysis of the lower extremities, and absence of sphincter control. The baby died twenty-eight days after birth.

Postmortem examination revealed an emaciated female infant with an enlarged head and widely open sutures and fontanelles. The lower extremities were flexed at the hips and fully extended at the knees with fixation of these joints. Both feet were dorsally flexed and inverted. The posterior arches of the lumbar spine were absent and in this region there was a small soft protuberance 1.5 cm. in diameter over which the skin was ulcerated. Removal of the central nervous system revealed fibrous adhesions and areas of purulent inflammation in the region of the roof of the fourth ventricle. It was further evident that there was an outpouching of the meninges in the area of the spina bifida and that the spinal cord and the cauda equina were included in this sac. A prominent hydrocephalus was noted on opening the brain. All the ventricles were dilated and the cortex was thinned in some places to 5 mm. Microscopically, an acute leptomeningitis and ependymitis were seen.

Major Anatomic Diagnoses.—Lumbar spina bifida with myelomeningocele; arthrogryposis of the lower extremities; bilateral talipes calcaneovarus; fibrosis of leptomeninges of roof of fourth ventricle with infected hydrocephalus.

The last pregnancy was in 1946. She again spotted slightly during the early part of the pregnancy and was given progesterone and stilbestrol daily. Labor began spontaneously at term and a male infant weighing 4,042 Gm. delivered spontaneously. Findings at birth included a meningocele in the lumbar region, flaccid paralysis of the lower extremities, and absence of sphincter control. The hydrocephalus was progressive. Death occurred on the sixty-third day of life.

Autopsy revealed the body of a poorly nourished male child with a greatly enlarged head. The enlargement was most pronounced in the anteroposterior diameter. Both fontanelles and all the sutures were widely open. A defect of the posterior processes of the lumbar spine

THE OCCURRENCE OF SPINA BIFIDA AND HYDROCEPHALUS IN SIBLINGS

A Review of the Literature and Case Report

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OVERT spina bifida is an uncommon congenital defect which is estimated to occur only once in every 1,000 births.^{1, 3, 4} Its occurrence three times in the same family is extremely unusual. When such an anomaly appears once, the obstetrician is frequently asked to give his opinion as to the probability of its recurrence in subsequent pregnancies. It is the purpose of this paper to review the literature dealing with this question and to present a case in which spina bifida and hydrocephalus appeared in each of three successive term pregnancies.

A thorough search of the literature reveals only 22 reported families in which overt spina bifida occurred in siblings. The first reported case appears to be that of Pendleton in 1857, cited by Shulman⁵ and listed in the bibliography of Ingraham,⁶ in which spina bifida occurred in three children of the same mother. In 1870, Menzies⁷ in Edinburgh reported a similar case. Butler-Smythe⁸ observed a family in which three children had spina bifida and two more were hydrocephalic. Sachs⁹ reported that he had seen a family in which three children in succession had spina bifida. Pybus¹⁰ cites a family in which all four children had defects, two with overt spina bifida, one with spina bifida occulta, and one with an exaggerated postanal dimple. Woltman¹¹ reported two cases in which two siblings had spina bifida. Three families with two spina bifida children in each were reported by Cutler⁴; in one of these, two additional children had hydrocephalus. In an exhaustive study of congenital malformations made by Murphy,¹² forty families were observed in which there were two or more defective children. In two of these families, spina bifida occurred twice, and, in one family, three children were affected. Murphy¹³ also reported on nineteen families with multiple deformities, of which he had been informed by individual physicians. In one of these cases, spina bifida occurred in two children. Shulman⁵ reported a case of spina bifida with meningocele in two successive siblings, and Penrose,¹⁴ in a study of 137 families in which spina bifida had occurred, found three families in which the abnormality had occurred in two siblings.

Four sets of twins in which each individual was afflicted with spina bifida have been reported: Fry¹⁵ reported the lesion in dizygotic twins which he had observed. One of these babies also had an associated hydrocephalus. Another pair was reported by Wright,¹⁶ in 1899, in which both babies had a myelocele and were hydrocephalic. Quisenberry,¹⁷ in 1944, reported a case of uniovular twins with spina bifida and myelomeningocele. Another pair of identical twins was reported by Eskelund and Bartels,¹⁸ both children having spina bifida and several other malformations, but neither of which had hydrocephalus.

The present case makes a total of six in which spina bifida has occurred three times in the same family.

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was seen over which there was a large (7 by 4 by 3 cm.) thin-walled, fluctuant, and violaceous cystic sac. Examination of the brain showed a marked dilatation of the ventricles and a thinning of the overlying cerebral cortex. The skull showed numerous thin uncalcified areas. Microscopically, the sac in the region of the spina bifida was partially lined with nervous tissue.

Major Anatomic Diagnoses.—Lumbar spina bifida with myelomeningocele; severe hydrocephalus.

Discussion

A case is presented in which both spina bifida and hydrocephalus occurred in each of three successive term pregnancies. After the first pregnancy, the mother of this family sought the advice of her obstetrician regarding the possibility of such a malformation being repeated if she were to become pregnant again. Since the incidence of this defect is generally regarded as about one in one thousand, the possibility seemed remote that a repetition of this abnormality would occur in a second pregnancy. She was so advised. When the second term pregnancy resulted in the same type of defect, the physician was reluctant to advise further childbearing because of the apparent incompatible hereditary factors. However, the sincere desire of these intelligent parents for a normal living child appeared to justify another attempt, the results of which were the same.

In each of these three infants hydrocephalus accompanied the malformation of the spinal column. The association of these deformities has long been noted, and a satisfactory explanation for the cause of the hydrocephalus is not always apparent. In the infants in this case, the probable cause of the hydrocephalus was apparent in only the second child, in which meningitis in the region of the fourth ventricle might have caused an obstruction to the outflow of cerebrospinal fluid. In 1935, Russell and Donald¹⁹ suggested that an abnormality of the hindbrain known as the Arnold-Chiari malformation, which sometimes occurs in association with spina bifida, might be responsible for the development of hydrocephalus. In the case presented there was no autopsy evidence of this malformation in any of the infants.

It was mentioned above that the appearance of spina bifida in siblings is rare, only 22 cases having been reported. However, once this defect has appeared twice, the probability of a third occurrence is high, for among these 22 families a third spina bifida occurred five times. On the basis of the meager literature which is available, it seems safe to advise the parents of a single child with spina bifida that repetition of such a lesion is very unusual and the probability of a normal baby is good. However, it would also appear that the parents of two such children have far less assurance that this defect will not appear a third time, and should be advised accordingly.

Summary

The literature concerning the occurrence of spina bifida in siblings is reviewed. A case is presented in which spina bifida associated with hydrocephalus occurred in three children of the same parents. Comment is made concerning the probability of recurrence of this malformation in subsequent pregnancies of the same family.

previously born); prematurity, 27 cases; multiple pregnancy eight cases; cephalopelvic disproportion, eight cases; placenta previa, four cases; bicornate uterus, previous uterine suspension, polyhydramnios, hydrocephalus and monstrosity, six cases. No cases were attributed to pelvic tumors, excessive size of the fetus, the introduction of a uterine bag, dead fetus, or pure accident, such as the premature rupture of the amniotic sac when the fetus lies in an abnormal presentation. The latter may have been an unrecognized cause in some cases, however, occurring before the fetus had assumed its normal longitudinal presentation. The less important etiologic role played by cephalopelvic disproportion and pelvic tumors is emphasized in this series.

Material Analysis.—In this series, there were 18 maternal deaths, or 9.6 per cent, and 75 cases of morbidity, or 40.8 per cent (Table I).

TABLE I. MATERNAL ANALYSIS

	NO. OF CASES	PER CENT
Maternal morbidity	75	40.8
Maternal mortality	19	9.6
Maternal average days in hospital		12.5 days
Multipara	149	80.1
Primipara	30	16.1
Unknown parity	7	3.7

The average stay in the hospital was 12.5 days. The youngest patient was 15 years old and the oldest 44 years. There were 42 patients (23.4 per cent) 20 years of age or less (Table II).

TABLE II. MATERNAL ANALYSIS

MATERNAL AGE	NO. OF CASES	PER CENT
(Youngest patient, 15 years)		
(Oldest patient, 44 years)		
20 years or less	42	23.4
21 through 30 years	68	37.9
31 or over	69*	38.5
Age not given	7	

*Of which 41 were 35 years or above, or 22.9 per cent.

There were 68 patients (37.9 per cent) 21 through 30 years, and 69 patients (38.5 per cent) 31 years or above, of which 41 (22.9 per cent) were 35 years or above, showing the increasing incidence of transverse presentation with the later years of childbearing and associated with increased parity.

Diagnosis and Management.—In many of these cases, the diagnosis of transverse presentation was not suspected prior to rupture of the membranes and prolapse of the cord or an upper extremity into the vagina. The patient was admitted to the hospital in this condition in numerous instances after being grossly mishandled on the outside. In many instances, the correct diagnosis was not made before the membranes ruptured, although the patient was in the hospital at the time. In other instances, the membranes were ruptured, either accidentally or deliberately, by the examining physician in the presence of an incompletely dilated cervix, thereby jeopardizing the life of the baby to a much greater degree. Many patients came into the hospital after long labors on the outside with intrapartal infection, varying degrees of cervical dilatation, and often a dead baby from prolonged labor or a prolapsed cord. Very few cases had the benefit of x-ray in the diagnosis of presentation. Some patients were in the hospital for several days before labor started, and the condition might have been corrected by external version, had it been

TRANSVERSE PRESENTATION OF THE FETUS

An Analysis of 186 Consecutive Cases

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ALTHOUGH transverse presentation of the fetus has been a long-recognized abnormality, no extended series of this type of dystocia was analyzed before Eastman's paper in 1932.¹ Recently Alexander and Schneider analyzed a fairly large number of cases.² Prior to Eastman's paper, the Germans had been the main contributors to the literature on this subject, producing a long series of studies chiefly devoted to the optimum time for performing version in this abnormality. These covered a number of previous years when these cases were commonly handled by combined podalic version in all cases permitting the introduction of two fingers through the cervix, followed by a period of waiting for complete cervical dilatation, when extraction was usually done. In 1886, Winter³ called attention to the high fetal mortality associated with this practice, unless conditions permitted immediate delivery, and recommended doing version only after the os was fully dilated.

This study covers a series of 186 consecutive cases of transverse presentation which have occurred in Charity Hospital of New Orleans, from 1906 through 1945. During this time there were 89,526 deliveries, giving an incidence of 1 to 481 cases. Following the example of Eastman, we have omitted from the series cases which changed to a longitudinal presentation, whether spontaneously or as a result of external version, as we are not certain in these cases whether we are dealing with a true example of this condition. Eight cases of twins are included, in seven of which the second twin presented transversely with a prolapsed upper extremity in the vagina after the first baby had been delivered at home by a midwife. The other case was admitted with an upper extremity of the first twin in the vagina. Consequently all eight cases presented a true example of transverse presentation in one of the twins. The purpose of this study is to analyze the factors producing dystocia and the high associated fetal mortality, as well as the high maternal mortality and morbidity.

Etiology.—There were only 30 primiparas in the series, or 16.1 per cent of the total number of cases, although the clinic population of primiparas is usually near 50 per cent of all admissions. The striking role played by multiparity is shown in that 82 of the patients with this abnormality, or 44 per cent, had had three or more previous babies; 39, or 20.9 per cent, had had six or more; 14, or 7.5 per cent having had nine or more babies. The latter group comprise only a very small per cent of the total number of women delivered.

Of these 186, the etiology may be given, alone or combined, as multiparity (women having had three or more previous children), 82 cases; unknown, 54 cases (of which 26 were multiparas with no record of the number of babies

TABLE IV. CAUSES OF FETAL DEATHS

	NO. OF CASES	NO. OF FETAL DEATHS	PER CENT
1. Early rupture of membranes prior to 7 cm. dilatation	138	92	66.6
2. Premature rupture of membranes before labor	28	21	75.0
3. Prolapse of cord before delivery	40	29	72.5
4. Prolonged Labor			
a. Delivered within 12 hours of onset of pains	53	22	41.5
b. Delivered within 12 to 24 hours of onset of pains	49	26	53.0
c. Delivered after 24 hours of onset of pains	63	58	92.0
5. Admitted with ruptured membranes	114	90	78.9
Admitted with unruptured membranes	67	25	37.3

When delivery was attempted in the home, in 70 cases, there resulted 55 (78.5 per cent) fetal deaths. The extreme importance of maintaining the membranes intact during the first stage of labor in transverse presentation is strikingly shown in the 67 cases admitted with intact membranes, resulting in 25 (37.3 per cent) fetal deaths, while 114 patients admitted with ruptured membranes lost 90 (78.9 per cent) babies. As to the type of delivery and fetal loss, there were 139 patients delivered by version and extraction with 90 fetal deaths (67 per cent), while the 16 patients delivered by cesarean section lost 4 (25 per cent) babies.

In order to compare the results in the management of this abnormality, the whole group was divided into three sections of 62 cases each. In the first 62 cases (beginning 1906), there were 11 maternal deaths and 46 fetal deaths; in the intermediate 62 cases, 3 maternal deaths and 39 fetal deaths; in the most recent 62 there were 4 maternal deaths and 31 fetal deaths. Fifteen of the 16 cesarean sections were done in the last 62 cases. Though definite improvement is shown down through the years, there is room for considerably more in the last 62 cases.

Treatment.—Treatment should be based primarily upon: (a) early diagnosis of this abnormality of presentation, which is attainable only when one strives to make an accurate diagnosis of presentation in every woman at the beginning of labor. The x-ray should be used when in doubt; (b) external version, which may be possible before labor or early in labor, before the rupture of the membranes; (c) preservation of the bag of waters after labor starts until full dilatation, if possible, by avoiding artificial rupture, voluntary bearing down on the part of the patient, and possibly by the insertion of a vaginal (not intrauterine) bag at times, as recommended by Eastman, to make counterpressure against the membranes; (d) version and extraction only after complete dilatation of the cervix.

Cases presenting premature or early rupture of the membranes, with an undilated, thick cervix and a viable baby are best treated by cesarean section. Cases similar to these, but having had a number of hours of labor and a number of examinations, with the baby still in good condition, may also be sectioned by the Waters' technique if more children are desired, or by a Porro section if the patient is a multipara with several living children. Neglected cases with a dead fetus impacted in the pelvis are probably best handled by decapitation and delivery from below. Neglected cases with intrapartum infection in the presence of an undilated cervix may require hysterectomy on the unopened uterus, as a desperate resort. The free use of penicillin and sulfonamides in potentially or frankly infected cases is indicated.

Finally, the requirements for versions are emphasized as being a completely dilated cervix, no disproportion, a sufficient amount of amniotic fluid,

recognized. Seven cases of twins occurred in which the midwife delivered the first baby alive in the home and then sent the patient to the hospital because she was unable to deliver the second transverse twin. Five of these were stillborn.

Several cases had the membranes ruptured artificially to induce labor for various reasons without the attendant's realizing that he was dealing with a transverse presentation. The method of delivery was version and extraction in most of these cases but no instance was found where a manual examination of the uterus was made for possible rupture, although the latter was probably the cause of death in several instances, some proved by autopsy.

As in Eastman's series, cervical dystocia associated with incomplete dilatation after many hours of labor with ruptured membranes undoubtedly was responsible for much of the high fetal and maternal mortality. When these factors were combined with inadequate supervision of labor in the home and late admission to the hospital, intrapartum infection, death of the fetus in utero, and rupture of the uterus resulted in many instances. A typical case of such care is demonstrated in the following brief history.

CASE 4.—Unit No. 38-29055. The patient was a 29-year-old Negro para 6, who came to the hospital after several days of labor with a midwife in attendance. She had a dead baby with a prolapsed cord and was exhausted. Upon examination she was found to have a ruptured uterus with the baby free in the abdominal cavity. A laparotomy was done and the dead fetus and uterus removed. She expired on the second postoperative day of peritonitis in spite of blood and chemotherapy.

Analysis of Fetal Deaths.—Of the 186 babies weighing 1,500 Gm. or more, there were 27 cases in which the fetus was considered premature but viable, in that the weight was between 1,500 and 2,500 Gm., and the remaining 159 babies weighed 2,500 Gm. or more. Those weighing less than 1,500 Gm., although there were a number in the records, were not included, but classified as abortions.

Of the 27 prematures, there were 21 deaths, giving a mortality of 77.7 per cent while there were 99 deaths in the 2,500 Gm. or above group, giving a 62.2 per cent mortality. The corrected fetal mortality of both, omitting monsters, was 67.6 per cent. Of the 91 cases showing heart tones present on admission (Table III), there were 36 subsequent fetal deaths, or 39.5 per cent. Of these, 16 were delivered by cesarean section with four fetal deaths, or 25 per cent, and 75 delivered vaginally with 32 deaths, or 42.6 per cent.

TABLE III. ANALYSIS OF FETAL DEATHS

	NO. OF CASES	NO. OF FETAL DEATHS	PER CENT
Fetal heart tones heard on admission	91	36	39.5
Delivery by cesarean section	16	4	25.0
Delivered vaginally	75	32	42.6

As to the causes of fetal deaths (Table IV), early rupture of the membranes with 7 cm. or less of cervical dilatation (138 cases) was associated with 92 deaths, or 66.6 per cent. In 28 cases having premature rupture of the membranes, there were 21 deaths, or 75.0 per cent. There were 40 cases having prolapsed cords before delivery, with 29 (72.5 per cent) fetal deaths. The influence of the duration of labor in fetal mortality is emphasized in that, of 53 cases delivered within twelve hours of the onset of labor, there were 22 (41.5 per cent) fetal deaths; 49 cases delivered in between twelve and twenty-four hours of labor, resulted in 26 (53.0 per cent) deaths; while 63 cases delivered after twenty-four or more hours of labor resulted in the extremely high fetal loss of 58 (92.0 per cent) cases.

DYSONTOGENETIC MIXED TUMORS OF THE VAGINA

With Report of a Case of Sarcoma Botryoides

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SARCOMA botryoides of the vagina in children has been reported 81 times since Guersant reported the first case in 1854. Because of the rarity of this condition the reporting of another case was thought to be worth while. In 1944, Dwyer¹ reported the most recent case, and gave a fairly complete review of the literature. He pointed out that McFarland's articles,² together with their associated bibliography, are the most comprehensive to that date.

A search of textbooks on gynecology, pediatrics, and pathology reveals little information regarding these rare and interesting tumors. It is interesting to note that this particular type of vaginal tumor has been reported only in individuals under 22 years of age, with 60 per cent occurring under two years. There is no adequate explanation for this fact.

Etiology

McFarland stated that these tumors should be termed dysontogenetic, mixed tumors of the urogenital region. In collecting all the reports from the literature in 1935, he found a total of 74 cases confined to or primarily in the vagina, also a bewildering terminology containing 119 different names. He advocated the above term in an effort to clarify the situation and to include the entire class of neoplasms occurring in the urogenital system. He reasons that without the presence of indubitable muscular or cartilaginous elements or some other evidence of heterologous structures could they be correctly called mixed tumors. Of course he found many which were distinctly mixed tumors with a great divergence of appearance and structure, some firm, dense, fibroid, muscular, cartilaginous, or even osseous. Many others were soft, edematous, myxoid, polypoid, and cystic (botryoides) and it is this latter type that is considered at this time. As to etiology, McFarland thinks they should be regarded as springing from dislocated residual embryonal cellular material in close proximity to those structures that enter into the formation of the urogenital sinus. They should not be regarded as metaplasia as a rule, however, he does believe that some are homologous and arise from tissue elements normal to the part in which they occur.

Clinical Characteristics

Occurring predominately in early life, these tumors occur as a polypoid, grapelike mass filling the vagina and often protruding through the hymen. Many of these polypoid outgrowths contain cystic fluid due to edema, which causes them to present an almost transparent fleshy appearance, often dark red from intratumoral bleeding. Histologically, the vast majority are in an undifferentiated form consisting of round cells or spindle cells of a malignant nature, only rarely showing a more benign type. There is a thin layer of submucous connective tissue beneath which is the stroma of the tumor itself. At

and a sound uterus. As stated by Eastman, the intrauterine bag as a means of cervical dilatation in early rupture of the membranes is usually very unsatisfactory, as it repeatedly fails to effect dilatation after hours of use and predisposes to "hour-glass" contraction of the uterus and intrapartus infection.

Summary

1. One hundred eighty-six consecutive cases of transverse presentation at Charity Hospital, New Orleans, La., are analyzed.

2. The factors producing the high fetal and maternal mortality are emphasized.

3. Two factors seem essential from a study of this series in the possible lowering of maternal and fetal mortality:

- (a) An early diagnosis of the malpresentation present, and
- (b) The more frequent use of cesarean section in early labor in these cases.

4. Transverse presentation, although occurring about one-half as frequently as placenta previa, produced a much higher fetal loss than the latter in this series. In fact, the fetal loss is only exceeded by the loss associated with rupture of the uterus. Any obstetric abnormality producing a 67.6 per cent fetal loss and a 9.6 per cent maternal death rate over a period of years deserves the most serious consideration.

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The patient was admitted to Southern Baptist Hospital on Sept. 17, 1944, and the following morning under drop ether anesthesia, the hymen was dilated to admit the index finger easily. The growth was found to be attached by a broad base along the posterior vaginal wall in the midline from just below the cervix to a point just above the hymeneal ring. The cervix and rest of the vagina were free of growths, when inspected after exposure with small right angled retractors. The tumor was easily curetted off at the base and the latter cauterized as deeply as possible, considering the proximity of the rectal wall. The pathologic report was rhabdomyosarcoma (Figs. 1 and 2).



Fig. 1.—Low power showing stratified squamous epithelium on surface.

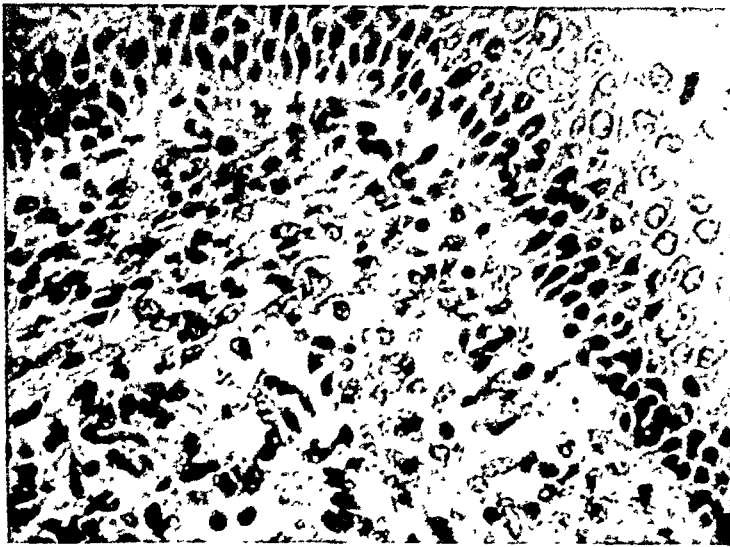


Fig. 2.—High power sarcoma botryoides of vagina.

The child subsequently received deep x-ray therapy. Radium was not used as it was felt that an effective dose could not be given due to the proximity of the rectal wall. Also to be considered was the technical difficulty of maintaining the radium in position were it used. The growth rapidly recurred within three months and again was protruding from the vagina as a necrotic, bleeding, friable mass, and the child rapidly declined in general health. Urinary obstruction, frequent hemorrhages, and terminal edema of the lower extremities preceded death, which occurred six months after she was first seen. No autopsy was obtained.

times there may be large elements in whose protoplasm a delicate striation is visible, hence the name rhabdomyoma or rhabdomyosarcoma is given.

These tumors are further characterized by being extremely malignant, recurring rapidly after all known forms of treatment. They do not metastasize widely but grow by extension to the bladder and peritoneum, obstructing the urethra and bladder as well as the rectum. In the terminal state, they are foul and necrotic and cause frequent hemorrhages. Death usually results from uremia, infection, or hemorrhage. The prognosis is uniformly bad, death resulting usually within one year. The mortality rate for the entire group reported in the literature is over 95 per cent.

One case reported by Engelmann³ in Germany in 1941 was apparently cured by radium.

Of the 31 cases analyzed by Neurnberger,⁴ 16 were found springing from the anterior vaginal wall, 10 from the posterior wall, and 5 from the lateral walls.

Incidence

As stated above, a search of the literature reveals 81 cases of these vaginal tumors reported to date. However, there seems to be some discrepancy in this total number, since Curtis states that there were but 31 well-authenticated cases. However, McFarland, in 1935, states that there were 74 reported cases of the very soft and simple botryoides tumors of the vagina all occurring before the twenty-second year. In addition to these 74 cases, seven more were found, the last being Dwyer's case reported in July, 1944. The case here observed brings the total reported cases to 82. (Since this report was made in 1945, a few more tumors of this type have been reported.)

Treatment

Since the usual course of the tumor is, as in the case of the botryoid type, repeated recurrence, local invasion of the surrounding tissues, and death from obstruction of the urinary passages, little can be expected from operative treatment, and in almost all cases it fails, and the patient dies. Treatment by x-rays and radium offers no more. However, the case of Engelmann, in which radium was implanted into the tumor area and an apparent cure effected, is noteworthy.

Case Report

C. N., a girl, aged 22 months, who was first seen Sept. 10, 1944, presented a "bloody vaginal discharge." The discharge had been present for about two weeks and was of a light watery nature and non-irritating. Historical review by systems was lacking of any noteworthy findings. She had been a normal full-term infant at birth and had had none of the usual childhood diseases. She was the first born of apparently healthy parents with no family history of malignancy.

Physical examination showed a well-developed and well-nourished, ambulatory white child, apparently in excellent health. The temperature, pulse, and respiratory rate were within normal limits. The general physical examination was negative. Examination of the vulva revealed a thin, pinkish, watery discharge. When the child cried, a mass of pale, reddish, edematous, polypoid tissue protruded from the vagina, receding from view when she relaxed. A finger in the rectum could easily cause a large amount of this mass to protrude. The growth was friable, soft, bled easily, and was considered to be possibly a cervical or uterine polyp which had prolapsed at the introitus by a long pedicle. The pelvic organs could not be felt by combined rectal and abdominal palpation. No abnormal masses were noted otherwise in the pelvis. No abnormalities of the rectum were present. The blood count, sedimentation rate, and urine were normal, and the Wassermann was negative.

MANAGEMENT OF CHRONIC ENDOCERVICITIS IN INFERTILITY

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ONE of the requisites of absolute fertility is that the endocervical secretions be favorable to spermatozoa. Normally, the endocervical mucus enhances sperm migration. The endocervix is comprised chiefly of compound racemose glands lined with high columnar epithelium. These glands secrete mucus which undergoes cyclic changes, and is under the hormonal control of the ovary.^{1, 2, 3} Abarbanel⁴ not only observed these cyclic variations, but duplicated them in castrated women by means of estrogens alone and in combination with progesterone. Associated with the relatively rapid preovulatory increase in biologically active and available estrogens, there is a corresponding increase in the volume of the cervical mucus and a marked diminution in its viscosity. When the viscosity is least, sperm migration is greatest in number, ease of penetration, and duration of motility in the mucus. Following ovulation, the volume of cervical mucus decreases, the viscosity rapidly increases, and the spermatozoa are ordinarily unable to penetrate the mucus. It should be emphasized that because of these physiological variations, post-coital studies for sperm migration should be done at the estimated time of ovulation.

The endocervical mucus may become so altered as to be definitely hostile. This hostility to spermatozoa may impair motility and penetration.

Hamblen⁵ lists the causes of cervical hostility as an abnormally viscid endocervical secretion resulting from chronic pelvic congestion, scanty coital secretion, endocervicitis, and poor cervical drainage with inspissation of the mucus plug due to a pinpoint external os. Chemical hostility (lowered pH) of endocervical secretion may result from infection and poor drainage. The cervix may be hostile due to incomplete cyclic preparation for insemination because of ovarian failure.

Chronic endocervicitis is probably the most common gynecologic disorder in women.⁶ Fulkerson⁷ checked records of 6,483 women examined in the gynecologic department of the Cornell University Medical School and found a diagnosis of cervicitis or endocervicitis in 33.16 per cent. Some authors⁸ estimate the incidence of chronic cervicitis to be as high as 80 per cent. That chronic endocervicitis is a common cause of sterility has long been observed. It is the opinion of the authors that this condition is the most common cause of sterility, and that its importance has not been sufficiently emphasized. Reis and Bernick⁹ state that cervical disease is the most common cause of sterility

Summary

A case of sarcoma botryoides (rhabdomyosarcoma) of the vagina is reported in a 22-month-old child, and a review of the literature is given, and the etiology, nomenclature, etc., are considered. Much confusion exists as to etiology and nomenclature and McFarland's work has done much to clarify the situation.

These tumors are rare, many frequently occur in early life, and are almost invariably fatal in a relatively short time, as all the potentially malignant, and most of them actively so.

This class of tumor is thought to be relatively resistant to irradiation, although one case was apparently cured by implantation of radium needles. Surgical extirpation is followed by rapid recurrence as a rule.

I should like to express here my appreciation to Dr. Emil Novak for examination of specimens of this tumor, and his comments thereon.

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1430 TULANE AVENUE

During the past two years our attention has been directed toward the treatment of chronic endocervicitis with the intramuscular injection of penicillin in oil and wax as an office procedure. Recently, several investigators^{13, 14} have reported encouraging results with the local application of penicillin in the treatment of cervicitis. Penicillin is also being used successfully in the treatment of pelvic inflammatory disease.^{15, 16} One of us had the privilege of discussing a paper presented by Professor H. Lloyd of the University of Birmingham at the International Congress of Obstetrics and Gynecology recently, in which she analyzed comparative results using sulfonamides and penicillin in the treatment of sterility. She used a single dose of penicillin, 300,000 units, and reported successful results in 17½ per cent of her patients, in contrast to 20 per cent with the use of sulfonamides.¹⁷

The purpose of this communication is to report a series of 55 consecutive patients with chronic endocervicitis treated with this drug.* All patients selected for treatment had a thick, viscid, mucopurulent discharge escaping from the cervical canal. Bacteriologic and sperm migration studies of the cervical mucus were made.

Method

Our technique of administration and dosage of penicillin has varied somewhat as we have had opportunity to observe our results. Originally 300,000 units of penicillin-oil-beeswax† were administered into the gluteal muscles as the initial dose and two subsequent injections of 200,000 units each were given on alternate days. Our present procedure is to administer 300,000 units daily for three consecutive days for a total dosage of 900,000 units. Occasionally, it has been deemed advisable to repeat with a second similar course.

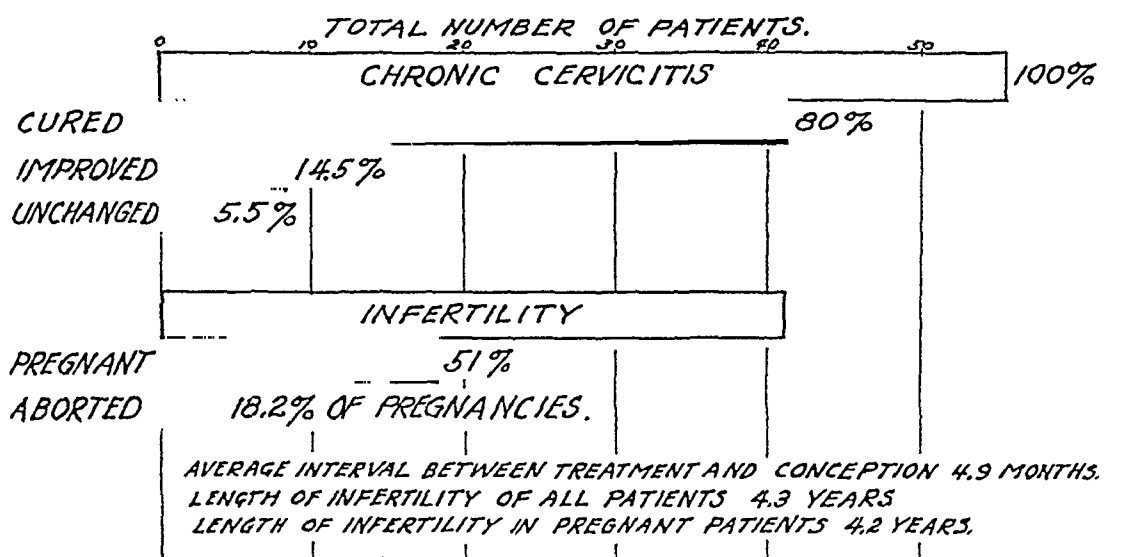


Fig. 1.

Results

A total of 55 patients with chronic endocervicitis was treated. Forty-one of the women consulted us because of infertility. The remaining fourteen, many of whom were single, did not desire pregnancy (Fig. 1).

*This series has been increased to over 200 cases with almost identical results.

†We now use procaine penicillin in sesame or peanut oil instead of beeswax.

in women, finding its existence in 60 per cent of 125 consecutive private patients examined. Fifty-six of these patients with cervical disease had endocervicitis. This was almost three times the frequency of salpingitis.

It is not our desire to discuss in detail the pathology of chronic endocervicitis, but it is important to emphasize that, in the presence of infection, the irritation stimulates the mucous cells to a hypersecretion with a marked increase in viscosity. Considerable study of sperm migration in mucus secreted from an infected cervix discloses that penetration is frequently either poor or absent, even at mid-cycle. This is not due to the presence of leucocytes, but is the result of a loss of fluid which accompanies the infection and increases the viscosity of the secretion from the endocervical glands.

Some degree of parametritis, perisalpingitis or salpingitis, and oophoritis is frequently associated with chronic endocervicitis, because of the ascending lymphangitis. This contributes to the sterility problem. It is highly doubtful that gonorrheal infection is as frequently a cause of chronic endocervicitis as has been commonly supposed. Traumatism of labor or abortion is a common predisposing cause. The infection in the cervix is usually mixed, with the streptococcus and staphylococcus predominant, and less commonly the colon bacillus, pneumococcus and various vaginal parasites. Our studies tend to confirm this impression.

No attempt will be made to evaluate in detail the various methods of treatment of chronic endocervicitis. To date, no one procedure fulfills all requirements for a cure of this infection. Electrotherapeutic measures such as cauterization, coagulation, and conization, and ionization with copper or zinc have been used with varying degree of success. These methods have certain disadvantages in dealing with sterility problems since they are aimed primarily at the destruction of the diseased cervical glands. Since normal endocervical secretions play an important role in sperm migration, a procedure directed at the infection itself and the conservation of functioning normal glands is highly desirable. Occasional beneficial results have been obtained with dilatation and curettage. Major surgical procedures such as trachelorrhaphy, low cervical amputation, Sturmdorf's tracheloplasty, Schröder's repair and high cervical amputation seldom are the procedure of choice in dealing with sterility.

With the advent of chemotherapy, a more desirable method of treatment of endocervicitis became available. Sulfonamides, both orally and locally, have been used by many investigators.¹⁰ Palmer and Palmer¹¹ report 40 to 50 per cent success in curing endocervicitis, using one or two courses of sulfathiazole orally (6 Gm. daily for five days). When this treatment failed, a 10 per cent sulfapyridine solution was instilled into the glandular zone of the cervix with an improvement in their results. Dill¹² reports successful results by combining stilbestrol with sulfadiazine therapy. He believes the rationale of this therapy to be a combination of estrogenic enhancement of the resistance of the cervical mucosa with stimulation of overgrowth and the antibacterial effect of the sulfonamide drug. We have used sulfonamide therapy for many years with fairly satisfactory results.

cases, four spontaneous abortions occurred. This closely approximates the incidence of spontaneous abortion in an average group of obstetric patients.

Our bacteriologic studies again confirm the fact that the organisms present in chronic endocervicitis are a mixture predominantly of streptococci and staphylococci, and less commonly *B. coli* and pneumococci. In only one instance was the gonococcus proved to be responsible for the infection.

Sperm migration studies consistently revealed little or no sperm penetration even during the ovulation phase. Following treatment with penicillin-oil-beeswax, normal sperm migration was almost invariably observed.

Summary and Conclusions

1. Chronic endocervicitis is a very common cause of infertility.
2. Abortion, both spontaneous and induced, is an important factor in the etiology of chronic endocervicitis and sterility.
3. Bacteriologically speaking, chronic endocervicitis is most often caused by a mixture of the common pathogenic organisms other than the gonococcus.
4. Penicillin-oil-beeswax administered intramuscularly is almost a specific form of therapy in the treatment of chronic endocervicitis.
5. With the disappearance of the infection, there is a return of normal sperm migration in the endocervical secretions.
6. The use of penicillin-oil-beeswax is a valuable therapeutic agent in the management of the sterility problem.

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Of the 55 patients with endocervicitis, 44 (80 per cent) were cured and 8 (14.5 per cent) were improved. Only 3 (5.5 per cent) patients showed no improvement. Twenty-one of the infertility problem patients conceived following penicillin therapy (51 per cent success). The average interval between penicillin therapy and conception was 4.9 months. To date, 4 of the pregnancies (18.2 per cent) have ended in spontaneous abortion. The average length of time of infertility for all 41 patients was 4.3 years. The patients who conceived following penicillin therapy had an average infertility period of 4.2 years, whereas the patients who have failed to conceive to date had an average infertility period of 4.4 years.

Discussion

The results in the treatment of chronic endocervicitis with penicillin-oil-beeswax were very dramatic. The response to this form of therapy is almost specific. In our hands, no other treatment has yielded such gratifying results, and there is the added advantage of its simplicity, safety, and conservation of the endocervical glands with no local tissue destruction. The unfavorable reactions of a more serious nature, which we encountered with penicillin-oil-beeswax, were generalized urticaria and high fever.* These occurred in only two of the 55 patients with no grave consequences. Not infrequently a local allergic reaction occurs at the site of injection, which is manifested by pain, redness, induration, and some itching. Hot, wet applications locally have proved effective. We have had no local abscess formation thus far. In patients who present a history of allergy, Benadryl or Pyribenzamine is given prophylactically. In our series, 16 of the patients had an associated chronic pelvic inflammation and all of these patients except one, showed definite improvement. In evaluating our results, we would like to emphasize the fact that there was practically no difference between the length of time of infertility prior to penicillin therapy in the 21 patients who conceived and the 20 patients who failed to conceive to this date.

Twenty of the patients in the sterility group presented a history of having been pregnant at least once before. In this group there were 12 successful pregnancies and 8 failures following treatment. Twenty-one of the sterility patients had never been pregnant before. In this group, there were 9 successful pregnancies following treatment and 13 failures. The male factor alone could definitely be held responsible for two of these failures. No patency tests were done on any patient with chronic endocervicitis until the infection was cleared up. Following penicillin therapy, only two patients had complete tubal occlusion which was confirmed by hysterosalpingography. Four of the patients had a definite cervical stenosis.

Our studies seem to indicate that abortion, both spontaneous and induced, plays an important role in the etiology of both chronic endocervicitis and sterility. A history of abortion was elicited in 15 of the 55 patients treated for chronic endocervicitis. Of the 41 sterility patients, 13 had had at least one previous abortion. In the group of 21 successfully treated sterility

*These have been almost eliminated since the use of procaine penicillin in oil.



Fig. 1.—This represents mole and wall of uterus. The line of contact between them does not show evidence of decidua, even though there is a narrow zone of fibrinoid degeneration, similar to the so-called Nitabuchs layer which usually represents dividing line between placenta and decidua. Relation of mole to uterus in this case is similar to that found in placenta accreta.



Fig. 2.—Shows invasive mole. High power field. Shows same relation between mole and wall of uterus as mentioned above. Note the very loose, almost liquified stroma of large chorionic villi, complete absence of blood vessels and evidence of excessive proliferation of chorionic epithelium which form not two but several layers.

INVASIVE HYDATIDIFORM MOLE*

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THERE is a small group of cases of mole about which pathologists will differ in the microscopic diagnosis and be unable to give us a positive diagnosis as to the relative malignancy of the molar tissue. To these cases such terms are applied as malignant mole, chorionadenoma destruens, or locally invasive mole. These tumors rarely, if ever, give rise to clinical evidence of metastasis; therefore, the prognosis is excellent, provided that the uterus is removed. They are characterized clinically by variable amounts of uterine subinvolution, postmolar bleeding, and usually persistently positive tests for chorionic gonadotropic hormone.

Chorionadenoma destruens, or locally invasive mole, may run a clinically benign course; but it is recognized that such a condition may ultimately kill the patient by uterine perforation, sepsis, or hemorrhage, even though there is no clinical evidence of metastasis.

Chorionepithelioma is such an exceedingly rare disease that even in some large clinics it has never been seen.

B. H., white, aged thirty-seven years, gravida iv, was first seen in the office May 10, 1946. She stated that she had noticed a brownish discharge on two occasions and that three weeks before her visit, she had felt a mass in the left lower abdomen. The mass was progressively enlarging and the pain becoming progressively worse.

A vaginal examination revealed a cystic mass approximately 8.5 cm. in diameter in the left lower quadrant and distinct fullness in the right lower quadrant. The cervix was soft and closed. Although her last menstrual period was February 14, the uterus was approximately the size of four-plus months.

On May 12, she was admitted to the Polyclinic Hospital because of severe pain in left lower quadrant of the abdomen. The preoperative diagnosis was that of a twisted ovarian cyst complicating pregnancy. She was operated upon May 15th. The uterus was found to be enlarged to the size of a four months' pregnancy; the left ovary was cystic, about 8.5 cm. in diameter, with one complete twist in the pedicle; the right ovary was also cystic and about 10 cm. in diameter. We performed a bilateral oophorectomy. (The pathologic report was luteal cysts of the ovary, some with hemorrhage.)

Five days later, the patient aborted a hemorrhagic mass on which the gross pathologic report was "hydatid mole." The microscopic pathologic report was "necrotic hydatid mole."

On May 25, a dilatation and curettage were performed, a small portion of mole was removed with a sponge stick, and the uterus was thoroughly curetted with a sharp curette and given a firm uterine packing. The pathologic report on this portion of mole and curetting was "hydatidiform mole with infection and anaplasia."

On June 1, the patient was discharged from the hospital, stating that she "felt very good, except for a little weakness." The cervix was closed; and the uterus was involuted to the size of a normal multiparous uterus, mobile and not tender. On June 12, she again came to the office, stating that she felt stronger and had no bleeding. The cervix was closed; the uterus was well involuted, mobile, and not tender. Arrangements were made for a Friedman test to be done within the next six weeks.

On July 22, she was readmitted to the hospital because of jaundice and a vaginal bleeding of one week's duration. She was markedly jaundiced, the conjunctiva and the whole body were deeply icteric, and the liver was apparently enlarged to one fingerbreadth below the costal margin. A smooth, tender swelling was just palpable above the symphysis pubis.

*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, April 27, 1948.

Pelvic examination revealed moderate free bleeding from the cervix, which was soft and patulous. The uterus was uniformly enlarged to about twice the normal size and was soft in consistency. An internist, called in consultation, instituted symptomatic treatment of the jaundice. X-rays of the gall bladder revealed no evidence of dye. The liver was not enlarged. An x-ray of the chest showed no evidence of metastasis in bony cage, pleura, or lungs. These findings confirmed the clinical diagnosis of obstructive jaundice; the etiology remained obscure and any connection with the pelvic condition, a matter of conjecture. The jaundice began to diminish under treatment, and, by August 2, we decided that clinical and laboratory findings permitted operation. The pelvic condition was not treated per se; the vaginal bleeding continued intermittently in small amounts. Several rabbits died before a Friedman test was completed, but finally, on July 31, a completed one proved positive. On a quantitative Aschheim-Zondek done elsewhere, a verbal report was given on "2,000 mouse units per litre of urine."

The preoperative diagnosis was that of chorionepithelioma, or recurrent hydatidiform mole. A total hysterectomy with bilateral salpingectomy was performed. The uterus was found to be uniformly enlarged and smooth. After it had been incised, we found, attached to the fundus, a small hemorrhagic growth about 4 cm. in diameter.

Pathologic Report: The microscopic examination shows uterus, tubes, and parametrial tissue. The uterus is invaded by chorionic masses covered by pleomorphic hypertrophic cells with hyperchromatic nuclei, some with bizarre shapes. Several areas show vascular channels dilated by atypical masses. The tubes show hyperemia, edema, hemorrhages, and polymorphonuclear and mononuclear infiltrations. The parametrial tissue shows similar changes as well as the presence of numerous foreign-body types of giant cells.

The pathologic diagnosis was chorionepithelioma of the uterus and cystic dilatation of the cervical glands. The slides were shown to two other pathologists, who diagnosed recurrent hydatidiform mole. Dr. Arthur Hertig stated that he had made a diagnosis of chorionadenoma destruens, with a good prognosis.

Follow-up.—On September 4, the patient came to the office and stated that she had no complaints. The vaginal vault was found to be well suspended with no thickening or tenderness apparent. An x-ray of the chest and long bones done on September 24 revealed no evidence of metastasis. On November 22, she came again and complained then of a feeling of depression. Her weight was 112½ pounds; she had had several abscessed teeth extracted. On March 17 she stated that she felt very well and had no complaints. Her weight was 126, a gain of 13½ pounds since her last visit. She slept well and had a good appetite. Her hemoglobin was 76 per cent. She had an occasional flush. The vaginal examination was negative, and the Friedman test of April 23, was negative. On June 21, she stated that she was feeling very well and had no complaints; her weight was 128 pounds. Hemoglobin 82 per cent, blood pressure 130/88, and the vaginal examination was negative. She was last seen November 5, she stated that she was feeling very well and had no complaints; her weight was 138½ (a gain of 26 pounds since her operation), hemoglobin 82 per cent, blood pressure 134/80, and the Friedman test of November 12 was negative.

Summary

This is a case of invasive mole treated by complete hysterectomy and removal of the remaining appendages. Although on the patient's first admission to the hospital, the possibility of a hydatidiform mole was considered, the primary cause of her admission to the hospital was abdominal pain on the left side and the presence of a progressively enlarging mass. Since removal of both ovaries would probably be followed by miscarriage, religious considerations precluded further interference. After spontaneous expulsion of the mole, curettage, and exploration of the uterus, bleeding ceased and the patient was discharged from the hospital. When she was readmitted suffering from jaundice, enlargement of the uterus, and vaginal bleeding, the picture was one of suspicious malignancy, probably chorionepithelioma. After the clearing of the jaundice and the negative x-rays of chest and long bones,

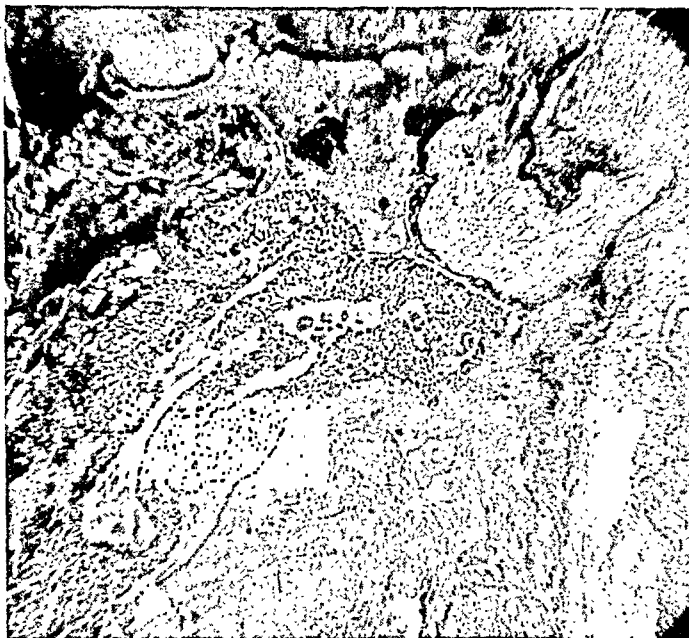


Fig. 3.—This shows more pronounced invasive tendencies of mole and close relationship between mole and myometrium. Note scarcity of villous pattern of mole which shows only in few instances formed villi. Most of the mole in this area consists of excessive overgrowth epithelium.

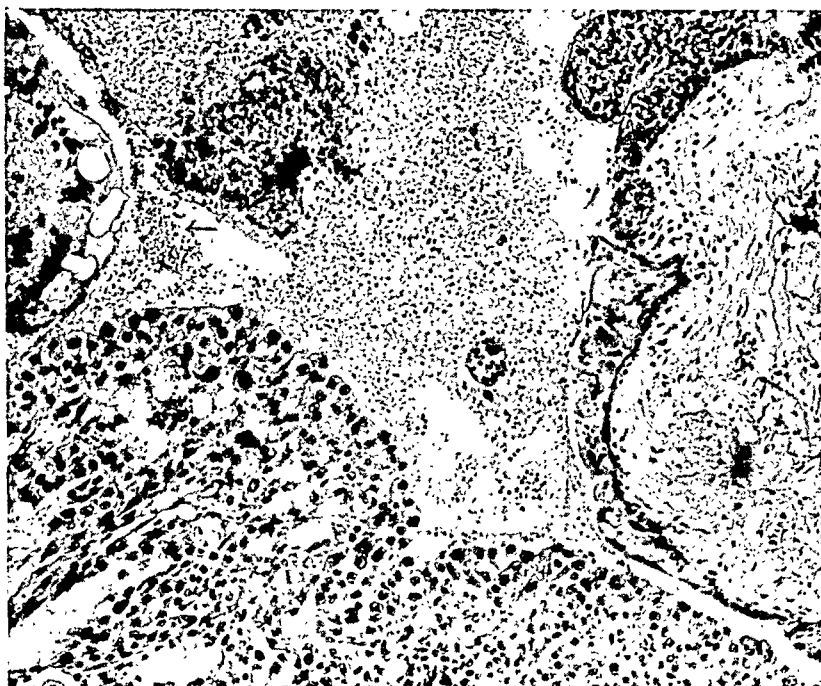


Fig. 4.—High power. This shows marked proliferation tendencies of chorionic epithelium which reveals striking resemblance to early trophoblast.

Arrow indicates a segment which shows very well the formation of syncytium. Rest of chorionic epithelium shows striking resemblance to cytotrophoblast.

GRANULOSA CELL TUMOR CONTAINING GLANDULAR STRUCTURES

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THE occurrence of glandular or tubulelike structures in granulosa cell tumors is unusual. The term "tubular" has been loosely used in the past to designate two distinct histologic types of granulosa cell tumors, neither of which contain tubulelike structures. Some authors speak of the columns of tumor cells between the stromal bands and cylinders of the cylindromatous granulosa cell tumors as tubulelike in arrangement. Others liken the exaggerated Call-Exner bodies in the microcystic folliculoid granulosa cell tumors to tubule- or glandlike structures. The tumors herein reported, however, are neither of the cylindromatous nor microcystic folliculoid type. Although Schiller¹ states that tubular structures have been observed in granulosa cell tumors and in the *folliculome lipidique* of Lecène, there is no record of this phenomenon in the available literature.^{2,3} A number of tumors originally classified as granulosa cell tumors with glandular or tubular structures have, upon re-examination, been re-classified as arrhenoblastomas or gynandroblastomas.¹ The case herein presented, however, fulfills many of the clinical and cytologic criteria of a granulosa cell tumor and must, therefore, be classified as such in spite of the unusual histology and somewhat atypical gross appearance and distribution.

M. L. (Hosp. No. 47-3277), a 67-year-old married white housewife, was admitted to Deaconess Hospital on the service of Dr. F. Hofmeister on June 23, 1947, complaining of vaginal bleeding and urinary dribbling, dysuria, frequency, and urgency. The vaginal bleeding began one month before admission, and initially consisted of but a small amount of bright red blood daily. The bleeding progressively increased in severity until at the time of entry when it was continuous. The patient had had seven children, and had experienced a normal menopause at the age of 50 years, seventeen years before admission. There had been no bleeding during this interval. The history was otherwise noncontributory.

Physical examination revealed a somewhat obese female. The blood pressure was 130/80, pulse 80, respirations 20, and temperature 98.6° F. The skin was soft and smooth, and the hair had a normal female distribution. The breasts were atrophic, and the patient had noted no recent changes in them. Remarkable physical findings were otherwise confined to the pelvis and perineum. There was some relaxation of the perineum with a moderate cystocele. The cervix was clean except for a small amount of blood in the os. The uterus was long, slightly enlarged, soft, and in normal position. A firm egg-sized mass was palpated bimanually in the region of the right ovary. The left ovary could not be felt.

All laboratory examinations were within normal limits. No hormone assays were done.

A preliminary diagnosis of adenocarcinoma of the endometrium was made but, because of the palpable ovarian mass, the possibility of a feminizing ovarian tumor was also entertained.

On June 24, 1947, the patient was operated upon under general anesthesia. A preliminary dilatation and curettage produced only a small amount of atrophic endometrium. The abdomen was, therefore, opened, and the bilateral ovarian tumors described below were found. The complete uterus, Fallopian tubes, and ovaries were removed.

The patient made an uneventful postoperative recovery. She was discharged on July 7, 1947, the fourteenth postoperative day. Nine months after discharge she was in apparent good health.

the markedly positive Friedman test and continued intermittent vaginal bleeding made a total hysterectomy with removal of the tubes appear the operation of choice, because a chorionepithelioma could not be discounted.

The final diagnosis is not easy. Two outstanding pathologists have examined the specimen carefully and feel that such invasiveness as can be found is definitely limited and not characteristic of a true epithelioma. Although the patient's course in the beginning was suspicious of malignancy, fortunately it turned out to be clinically benign.

Since it appears that there are various histologic or clinical grades of chorionic malignancy, rather than designate them all as chorionepithelioma, we must try to distinguish between them. Also, every patient harboring a hydatidiform mole should be individualized.

Management of these cases consists in the diagnosis and removal of malignant chorionic tissue while it remains localized in the pelvis and the avoiding of unnecessary surgery during the childbearing age because of the possibility that malignant chorionic tissue might be present. We must approach the problem very carefully, studying the clinical picture of each case, making a careful study of the microscopic traits of tissue that were removed or expelled, and making careful hormone studies. With critical evaluation of all factors, it will usually be possible to arrive at a more precise individual diagnosis.



Fig. 3.—(×700.) Small group of tubular glands.

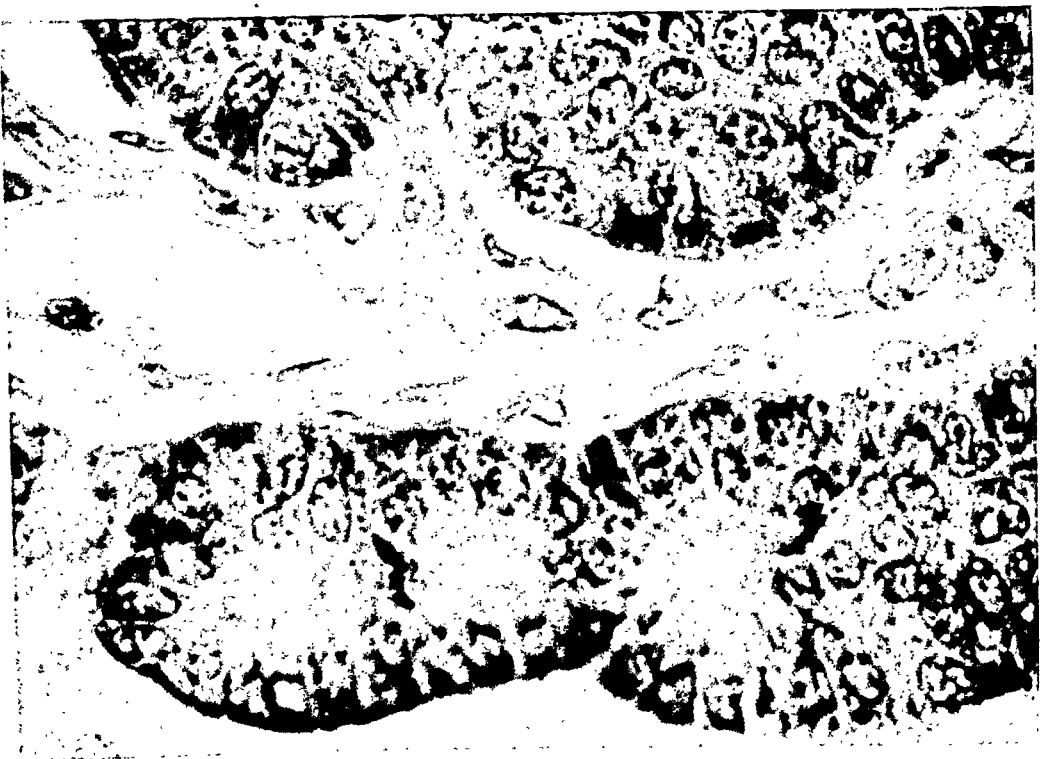


Fig. 4.—(×700.) Group of small glandular structures and the edge of a compact mass of granulosa cells.

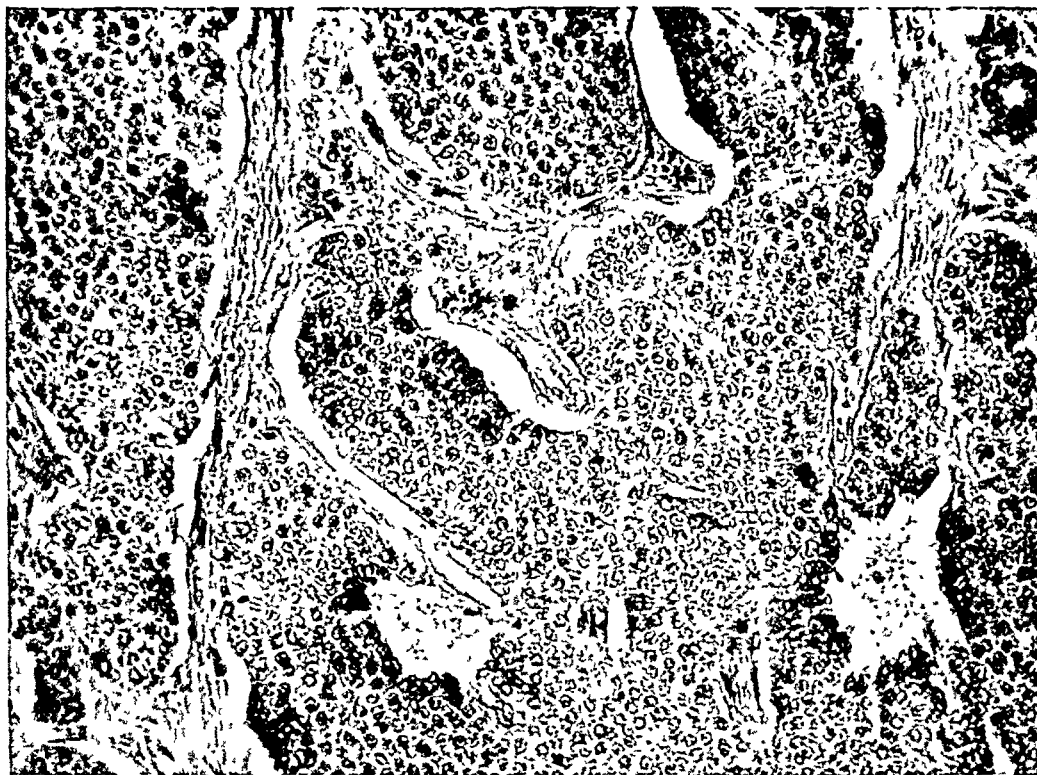


Fig. 1.—($\times 400$.) Parenchymatous masses of granulosa cells. Note the absence of Call-Exner bodies.

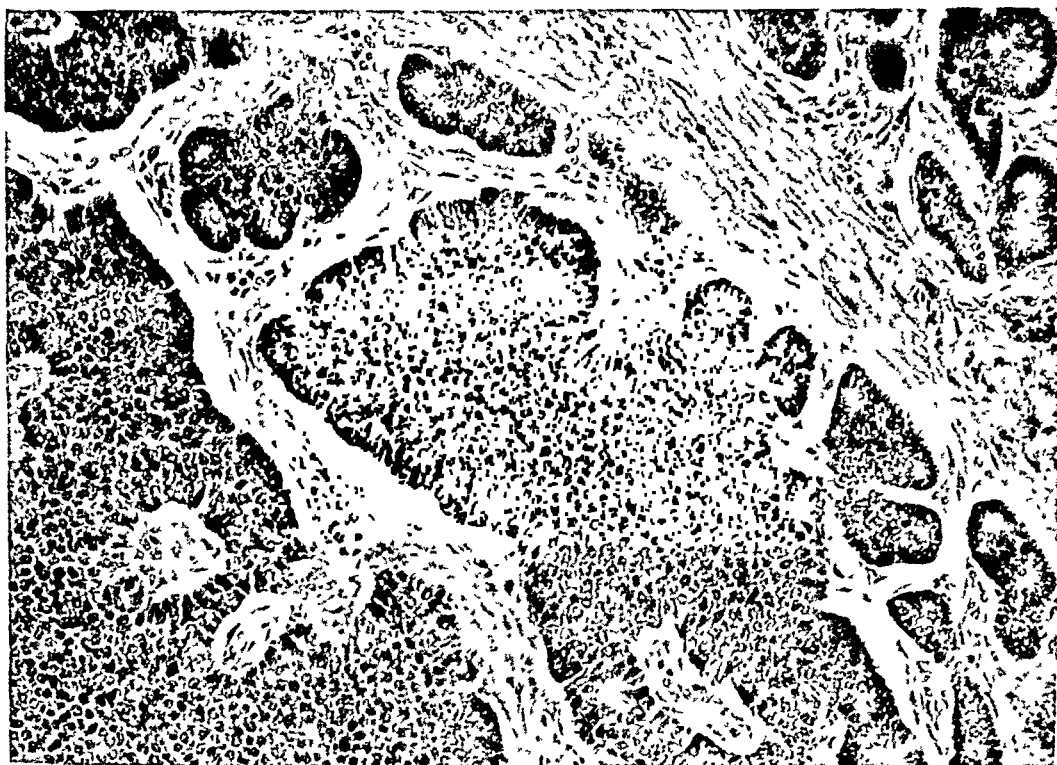


Fig. 2.—($\times 400$.) Masses of granulosa cells showing peripheral gland formation and glands in separate groups.

cases with adenopapillary proliferation of the glandular elements. Granting this assumption, these tumors might be classified as Lecene tumors prior to luteinization. The failure of luteinization is apparently due to an absence of the luteinizing gonadotropic hormone, Prolan B, in a woman of 67 years.

Summary

A case of bilateral granulosa cell tumors containing glandular structures is reported.

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Pathologic Findings

The specimen consisted of a few fragments of endometrium embedded in coagulated blood, and a complete uterus together with the tubes and ovaries. The uterus measured 11 by 5 by 3.5 cm. The surface was smooth. The myometrium was firm and somewhat thickened, measuring 1.5 centimeters. The endometrium was almost completely denuded. The endometrial surface was covered by a few shreds of recently coagulated blood. The cervix appeared normal. Both Fallopian tubes were thin and atrophic.

The ovaries were enlarged, smooth, and firm. The right measured 5 by 3.5 by 3 cm., and the left 4 by 3 by 2.5 centimeters. On section, both ovaries were almost completely replaced by well-circumscribed round tumor nodules: two in the right, 1 and 4 cm. in diameter, respectively, and one in the left, 3 cm. in diameter. The nodules presented a similar gross appearance. They were very well circumscribed and could be easily shelled out from the surrounding thin layer of compressed ovarian tissue. The cut surfaces neither bulged nor retracted, and were of a pale, definitely yellow color. The tumor tissue was slightly whorled and firm, except for several small areas of hemorrhagic softening.

Microscopically, the uterus displayed only a few fragments of atrophic endometrium in the proliferative phase. The myometrium showed atrophic changes of the senile type. The uterine curettings were few in number and essentially similar to the few fragments in the uterus. There was no evidence of endometrial hyperplasia, and the source of the uterine bleeding could not be determined.

All three ovarian tumor nodules were of identical microscopic structure. They were composed of small masses of tumor cells supported by a moderately abundant connective tissue stroma (Fig. 1). The masses appeared to shrink away from the stromal trabeculae. The tumor cells were small and stained moderately dark with hematoxylin. They displayed narrow halos of homogenous cytoplasm about small round or slightly ovoid nuclei. The chromatin network was rather coarse, and there were no nucleoli. Mitoses were rare. The cells were arranged in rather dense parenchymatous masses in some places but in others formed small glandular or tubulelike structures (Figs. 3 and 4). Here the cells were of a more columnar type with a small amount of cytoplasm on the luminal side of the basal nuclei. The glands were usually empty, but occasionally contained a small amount of pale pink material. They occurred at the periphery of the more cellular masses or in irregular groups and columns separate from the parenchymatous masses (Fig. 2). In no instance could they be found in the center of the masses. No Call-Exner bodies were found and the glandular structures bore no resemblance to them. The fibrous stroma of the tumor was moderately cellular. It was composed principally of elongated fibrocytes and a few younger connective tissue cells. The cytoplasm of these cells occasionally showed a fine vacuolization.

Fat stains on frozen sections were uniformly negative. Lipoid could neither be demonstrated in the tumor cells nor in the fibrous stroma.

Stains for argentophile cells using the Hamperl modification of Masson's silver method were similarly negative.

Comment

Were it not for the glandlike structures these tumors would be classified simply as granulosa cell tumors of the diffuse or parenchymatous type. This interpretation is strengthened by the history of postmenopausal bleeding and by the cytology of the individual tumor cells. The occurrence of glandlike structures, however, makes interpretation somewhat more difficult. The definitely yellow gross appearance, the arrangement of tumor cells in solid masses with peripherally located glands, and the occurrence of isolated columns and groups of glands all suggest a carcinoid tumor such as might be seen in the gastrointestinal tract. This possibility was seriously entertained, but repeated attempts failed to demonstrate the argentophilic nature of the tumor cells. Similarly, negative fat stains mitigate against a diagnosis of *folliculome lipidique*. Schiller, however, believes that the Lécène tumors develop in two phases; first, the establishment of the structure, and second, luteinization associated in some

The relief was immediate and dramatic. The patient appeared virtually deflated and comfortable for the first time. In a period of seven days, the patient made remarkable improvement. She was discharged free of her complaints and in good condition. There were no subsequent recurrences or sequelae. To avoid irritation of the tracheobronchial tree, smoking was strictly interdicted, and every precaution to avoid an upper respiratory infection was practiced.



Fig. 1.—Photograph showing areas of subcutaneous emphysema above and to the left of the inked line, anteroposteriorly.

Lightening occurred about the first of June, and labor began at 12:30 A.M. on June 13. For this case the management of the labor consisted of sedation of the mother during the first stage, employing a morphine sulphate-scopolamine hydrobromide routine; and in the second stage an elective forceps delivery as soon as feasible to particularly avoid bearing down because of the secondary strain that involves a pulmonary effort. Together with the latter thought to avoid any recurrence of the mediastinal and subcutaneous emphysema, it was necessary to choose an anesthesia that we believed might prevent the bearing down effort in the second stage and at the same time not irritate the tracheobronchial tree. Therefore, a low spinal anesthesia (saddle-block) was administered when the cervix was 8 cm. dilated. After thirteen and one-half hours of first stage labor, the cervix was completely dilated, and a female baby weighing 6 pounds 5½ ounces was then delivered by a low forceps aided by an episiotomy. Post partum course was uneventful, and the patient was discharged in good condition on her fifth hospital day. Six weeks follow-up found the mother and baby in sound health.

Discussion

Caldwell² has suggested that this clinical entity be called "Hamman's Syndrome" because of the excellent and extensive clinical material on this subject that was collected by Louis Hamman of Baltimore.

The pathologic anatomy of interstitial emphysema of the lungs was first described by Laennec.³ The first case was described by Simmons in 1783.⁴ Since then there has been a

PREGNANCY COMPLICATED BY MASSIVE SUBCUTANEOUS EMPHYSEMA OF MEDIASTINAL ORIGIN (HAMMAN'S SYNDROME)*

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ACUTE mediastinal emphysema is a rare and unusual complication in pregnancy. When it does occur, it might demand special types of medical, surgical, and obstetric management. The case reported herewith is the first known to have occurred on this obstetric service in the past twenty years. Air may reach the mediastinum by four routes: (1) along the fascial planes of the neck, (2) through a perforation of the tracheobronchial tree, (3) from the retroperitoneal space, and (4) from the interstitial tissues of the lung.¹ The following is the case report:

Mrs. A. P., a 19-year-old white primigravida, was admitted to the obstetric service of Cook County Hospital on March 17, 1947, at 9:25 A.M. Inspection revealed an apprehensive woman with cyanosis, dyspnea, gross puffiness of her face and neck, the left palpebral fissure three-fourths closed, and marked injection of both sclerae (Fig. 1).

History revealed the sudden onset of an almost continuous cough which began thirty hours before admission. This was followed by a smothering oppressiveness behind her sternum, associated with diffuse pains throughout her chest and shoulders. Respirations became rapid, and as the day wore on, she had to exert an active effort to breathe, which caused her to become alarmed. Sedation and cough mixture had little or no effect on the patient. Her rest during the night had been fitful, and the complaints continued unchanged. Previous medical, surgical, and familial histories were noncontributing. The expected date of delivery was June 15, 1947.

Upon examination, the most significant findings were an extensive subcutaneous emphysema which included the face and neck anteroposteriorly, the right side of the breast anteriorly, and the scapula posteriorly. On the left side this emphysema involved the trunk, the left shoulder, arm, and hand. Crepitation was palpated throughout all of these areas. The heart findings were normal. There was a gravid uterus at the level of the umbilicus. The fetal heart tones were 156 per minute. X-rays likewise showed this extensive subcutaneous and mediastinal emphysema (Fig. 2). The blood pressure was 112/50, the pulse was 92, the temperature was 98.6° F., and the respirations were 24.

At first the treatment was conservative, and included nasal oxygen, sedation, and supportive measures, together with watchful expectancy. After twenty-four hours the patient was more apprehensive, her respirations were more labored, and an extension of the subcutaneous emphysema now included practically all of her trunk. The patient was seen in consultation by Dr. Lindon Seed of the attending surgical staff. He advised an attempt to be made to release the emphysema through an incision at the manubrium sternum. This incision was made under local anesthesia; it was three-fourths of an inch in length over the manubrium sternum and released the air beneath the skin. Thus a large quantity of the entrapped air immediately escaped through this opening. Bubbles were formed in great profusion as the air rushed out. A rubber dam was sutured in the incision to allow more air to escape.

*Read before the Chicago Gynecological Society, Oct. 13, 1947.

A study of the literature reveals that mediastinal and subcutaneous emphysema, or Hamman's Syndrome, occurs in labor as one of the many possible maternal complications. Kosmak⁸ estimated the frequency of its occurrence as about one in 2,000 labors. He believes that "the complication occurs more often than this, but as it may pass off without appreciably marked symptoms, an emphysema of this kind, unless extensive, may readily enough escape the attention of the accoucheur." On our obstetric service the incidence of Hamman's syndrome in the gravid patient occurred far less often than the incidence estimated by Kosmak. An accurate rate of occurrence has never been kept; only a rough estimation at best can be made. To the best of my knowledge, the case here reported is the first to occur in any gravid woman before, during, or after labor on this service in the past twenty years, where approximately 100,000 mothers have been delivered.

It is generally agreed that there is a definite tendency for the mediastinal and subcutaneous emphysema to recur. This fact was acutely appreciated, and therefore a careful program of management was outlined for the delivery of this patient to present the best possible prophylaxis.

The majority of reported cases of Hamman's syndrome in labor have been in primiparous women of good health.⁹ Our case was a primigravida, who already had had an extensive and serious mediastinal and subcutaneous emphysema just three months before the onset of her labor. This was a definite challenge to the accoucheur. A recurrence had to be prevented. Three paramount prophylactic measures were followed: (1) to provide the maximum amount of maternal comfort and relief from pain with the minimal amount of harm to the newborn in the first stage, (2) to avoid any straining or bearing-down effort in the second stage, and (3) to avoid all pulmonary irritants. The methods used as described above proved equal to the demands of the labor, and the delivery was terminated with mother and newborn infant in good condition.

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growing interest on this subject, with special attention being focused on the differential diagnosis of this syndrome from other conditions presenting acute thoracic complaints.

The etiology of the mediastinal and subcutaneous emphysema in the present case reported was apparently due to the sudden onset of coughing which produced an increase in the intrapulmonary pressure, causing a forceful distention of the lungs. This has been offered as one possible cause for this entity by Hamman,¹⁻³ and Schwartz, McIlroy, and Warren.⁵ Joannides and Tsoulos⁶ have proved this in their experiments on the dog, and they have gone on to show the pathogenesis of this process, plus the possible very serious complication of an air embolism.

Classically, Hamman's Syndrome is characterized by (1) pain, (2) subcutaneous and retroperitoneal emphysema, (3) obliteration of cardiac dullness, (4) peculiar sounds heard over the heart such as crunching, crackling, or bubbling sounds with each contraction, (5) evidence of increased mediastinal pressure, dyspnea, cyanosis, engorged veins, circulatory failure, (6) pneumothorax, and (7) roentgenographic evidence of air in the mediastinum.¹ The case here reported meets all the clinical and laboratory demands of this condition, except that the heart was without findings.



Fig. 2.—Anteroposterior view of the thorax revealing extensive subcutaneous and mediastinal emphysema.

It is generally considered that the course of mediastinal emphysema together with its accompanying subcutaneous manifestation is mild.⁷ This is especially so when its etiology is not secondary to such primary factors as perforation of the trachea, bronchus, or esophagus, association with acute infections such as pneumonia, influenza, diphtheria, and whooping cough, or precipitated by bronchial asthma or tuberculosis. Rest and sedation are generally considered adequate measures of therapy in a benign and self-limiting process. However, when the emphysema is progressive, with extension and increase in the mediastinal pressure, there is an immediate need for decompression by the simplest and most expedient method. In our case, a single incision over the manubrium sternum gave an escape route to the entrapped air. The response to this simple procedure was almost instantaneous, with remarkable relief to the patient and obvious control of the disease process.

posterior half of the aorta from the aortic valve to the bifurcation and down the right common iliac artery. The intima of the aorta showed moderate arteriosclerosis but the rupture did not occur in an arterosclerotic plaque. The respiratory tract, gastrointestinal tract, liver and gallbladder, pancreas, and spleen were essentially negative. The kidneys were increased in size, the right weighing 260 Gm. and the left 200 Gm. The capsule stripped fairly readily. The surfaces were finely granular. On cut section, the cortico-medullary junction could not be discerned. Within the uterus there was a fetus which was consistent with an eight months' pregnancy. The right ovary measured 10 cm. in diameter and was fluctuant. On being sectioned, thick yellow sebaceous material poured from the cyst and within the wall of the cyst there were several calcified nodules.

Microscopic Examination.—*Cardiovascular system:* Many of the myocardial fibers appeared normal but some were swollen. There was stasis of blood and the small arteries within the myocardium showed thickened walls and moderate sclerosis of the intima. Sections through the coronaries show parts of them narrow with marked thickening of the wall, especially the intima, distortion of the elastic tissue, heavy deposit of lipid material within the intima and some calcification. Fibrosis involved some parts of the muscle in the thickened coronary. Elastic stains of the coronaries show extensive fragmentation of the elastic tissue within the wall, most marked in the region of the sclerotic plaques. Around the coronaries there is an infiltration with a moderate number of mononuclear cells. Sections of the aorta show severe medial disease in which there are numerous vacuoles and splitting of the muscle fibers in the outer third of the aorta. There is massive hemorrhage extending much of the length of the aorta but numerous vacuoles are shown in the media throughout most of the sections. In addition, there are a few zones in which fibrosis is evident, particularly in the inner parts of the aorta over areas which show arteriosclerosis. In most areas the elastic tissue is fragmented and small cysts around fragmented elastic fibers are widespread. There is diffuse hemorrhage in the periaortic tissue as well as the region of the split media. *Genitourinary System:* The kidneys show changes consistent with moderately advanced arterial and arteriolar nephrosclerosis. The ovary showed a benign teratoma. No significant changes were found in other organs.

Comments.—This is a case of a 35-year-old white woman in her eighth month of pregnancy who had severe hypertension, moderate arteriosclerosis, spontaneous rupture of the aorta into the pericardial sac, and dissection through the entire length of the aorta and into the proximal right common iliac artery.

The relationship of hypertension to the idiopathic medial necrosis is debatable. Schnitker³ reported hypertension in 50 per cent of his cases below the age of 40 and in two of eight who were pregnant. Rottino^{4a} has stated that dissecting aneurysms are found more frequently in patients who are hypertensive. He^{4b} also reported studies on aortas from 210 routine autopsies. He had 54 cases of hypertension in this group, of which 51 per cent showed medial degeneration. Karsner⁵ states, "The disease occurs in hypertension and this may favor rupture." Mote and Carr,⁶ however, found no clinical hypertension in 19 of 26 cases, but no postmortem findings were given concerning these cases.

Erdheim postulated that there may be a hyperepinephrinism in hypertension which might cause local spasm of the vasa vasorum with production of focal ischemia and necrosis in the aortic wall. Several workers have produced dissecting aneurysms experimentally in rabbits by repeated massive doses of epinephrine.

Leary and Weiss⁷ produced a dissecting aneurysm arising in an atheromatous ulcer in an animal fed a high cholesterol diet for a long period of time. No blood pressure determinations were available on this animal but in view of a hypertrophied heart and "chronic vascular nephritis" in one kidney, it is reasonable to assume that hypertension was present.

Schlichter,⁸ in 1946, attempted to prove the relationship between the vascularity of the aorta and necrotic lesions within the media. He cauterized the adventitia of dogs

MASSIVE AORTIC DISSECTION (DISSECTING ANEURYSM) ASSOCIATED WITH PREGNANCY AND HYPERTENSION

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SINCE Gesell¹ and Erdheim² first described "medionecrosis cystica idiopathica," it has been carefully studied by many workers. Until recently, dissecting aneurysms of the aorta have been considered limited to the older aged individuals. In a splendid comprehensive article, Schnitker and Bayer³ reviewed the literature and found 580 cases reported, of which 141, or 24.31 per cent, were under the age of 40 years. Forty-nine of these 141 cases were in women. Twenty-four of the 49 cases occurred in pregnancy, twenty of these in the last trimester, before labor began. Labor pains had begun in only two cases when rupture occurred. Only two patients of eight in whom blood pressure determinations were recorded showed evidence of hypertension. The author states that "this high incidence of pregnancy and dissecting aneurysms of the aorta in young individuals has not received widespread appreciation." We desire to present an additional case in a 35-year-old pregnant multipara.

Case Report

Mrs. T. Z., aged 35 years, gravida vi, para v, was dead on arrival at the emergency room of the South Side Unit of the Youngstown Hospital Association on Dec. 6, 1947. Her obstetric history showed full-term, uncomplicated pregnancies with living children in 1930, 1932, 1935, and 1938. On Nov. 4, 1939, she was admitted to this hospital in active labor, her last menstrual period having been Feb. 8, 1939. This pregnancy had been uncomplicated with the exception of a small abscess in the right breast. Her blood pressure was 140/100 and urinalysis showed a slight albuminuria. No enlargement of the heart was detected. She had an uncomplicated delivery of a full-term baby boy. Her postpartum course was uneventful. The breast abscess was incised and drained and she was discharged on her eighth postpartum day.

Oct. 8, 1947, nearly eight years after this fifth pregnancy, she consulted a physician in his office. Her last menstrual period was May 15, 1947. Examination showed a blood pressure of 230/116, pulse 104, and weight of 144 lbs. Urinalysis and Wassermann were negative. She returned for five office calls and constantly showed an elevated blood pressure but negative urinalysis. Her last office visit was Dec. 5, 1947, at which time her blood pressure was 232/150. She had a trace of albuminuria and edema of the ankles. She complained of pain in the back of several days' duration. She was given a sedative and complete bed rest was advised. Later that evening she complained of pain shooting down the back of the right leg. Both the pain in the back and leg were severe. The physician visited her at home and administered a sedative. Shortly thereafter she became nauseated. She started for the bathroom but suddenly collapsed and had a convulsion. She was quickly rushed to the hospital but was dead on arrival at the emergency room.

Autopsy.—Externally the abdomen was consistent with an eight months' pregnancy. When the thorax was opened, the pericardial sac was tense and contained approximately 500 c.c. of clotted blood. The heart weighed 600 Gm. On being sectioned, all chambers of the heart were thickened but this was most marked in the left ventricle. The valves were not unusual. Two cm. above the aortic valve on the anterolateral aspect of the aorta, there was a stellate tear in the intima which communicated with a large hemorrhage within the wall of the aorta. There was a communication between this and the pericardial cavity. The wall of the aorta was split. The dissecting aneurysm involved the

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If merely deficient vascularization is the cause of cystic degeneration leading to dissecting aneurysms, one would expect the deeper parts of the muscle to suffer more than those parts of the wall closer to the nutrient arteries. Experience has shown that the dissection is usually in the outer one-third⁹ where the nourishment should be relatively good.

The severe hypertension in our patient with excessive stretching of the aorta may have caused disturbance in the blood supply to the wall and rupture of the elastic fibers. Certainly, hypertension cannot be disregarded as an important factor in our case.

Grateful acknowledgment is made to Dr. Horace K. Giffen for his invaluable help and criticism, Mrs. Mary Miles for the photographs, and Miss M. Sokol for compiling material.

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and produced zones of necrosis within the media. He noted edema in the outer one-third with focal hemorrhages within twelve hours after coagulation. In the outer two-thirds of the media diffuse necrosis developed when the blood supply was destroyed, provided the collateral circulation was scanty. The inner one-third of the media, however, also showed necrosis and cyst formation even though this part of the artery is nourished mainly from the aortic lumen. In some of his cases, extensive necrosis resulted in aneurysms and occasionally local dissection. He did not succeed in reproducing the massive diffuse necrosis and dissecting aneurysm such as is seen in human cases.

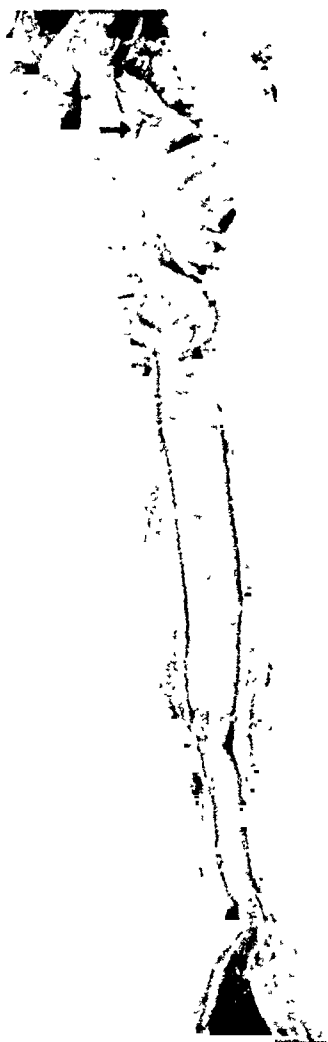


Fig. 1.

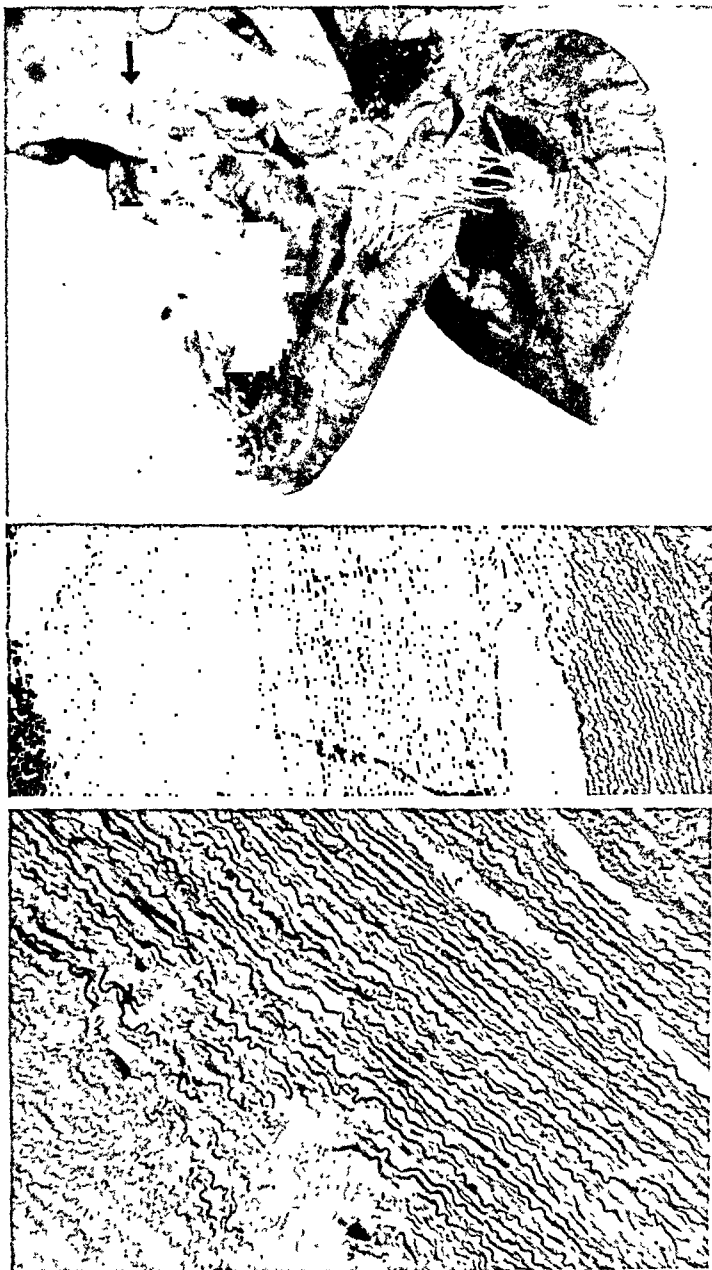


Fig. 2.

Fig. 1.—The aorta showing the site of rupture indicated by the arrow and posterior dissection of the entire length of the aorta and into the right common iliac artery.

Fig. 2.—A, Closeup of 600 Gm. heart showing the site of rupture 2 cm. above the aortic valve indicated by the arrow.

B, van Gieson elastic stain of the aorta showing intimal thickening, subintimal atheromatous deposits, disruption of elastic fibers and medial splitting with hemorrhage.

C, van Gieson elastic stain of the aorta showing fragmentation and loss of elastic fibers, loosely arranged fibrous scars and cystic degeneration of the media.

each 2 minims at thirty-minute intervals. Patient began to hemorrhage profusely and developed pains and strong uterine contractions every two to three minutes. The patient was taken immediately to the delivery room and a vaginal examination revealed the cervical os 3 cm. dilated and the fetal head presenting. Willett forceps were applied to the fetal head and continuous traction made; meanwhile, the patient was given 500 c.c. of plasma. After forty-five minutes, the forceps tore out and the examination at that time revealed the cervical os 8 cm. dilated and the placenta presenting at the internal os in front of the fetal head and completely occluding the os. At this time the patient was having continuous pains and contractions and, under ether anesthesia, the placenta was pushed aside and the membranes penetrated and an internal podalic version was performed and a premature male infant delivered by breech extraction, the placenta being delivered ahead of the breech. The baby was alive on delivery, but lived only eleven minutes. The patient at this time was in extremis from blood loss and was given 1,000 c.c. of whole blood and 1,000 c.c. of 5 per cent glucose in normal saline in addition to the 500 c.c. of plasma and left the delivery room in fair condition. Her condition improved, but on Sept. 25, 1947, her hemoglobin was 44 per cent and red blood cells 3,160,000. The anemia was treated with transfusions and hematopoietics and she made a steady and uneventful recovery, and on Oct. 4, 1947, her hemoglobin was 59 per cent and red blood cells 3,340,000. The patient was discharged on Oct. 5, 1947, in good condition, with fundus involuted normally for the postpartum period and her lochia normal. She was seen six weeks post partum at follow-up examination and her condition was normal at that time except for a moderate secondary anemia.

Discussion

This patient represents a true case of prolapse of the placenta. First, she had a vaginal examination prior to delivery and there was definitely no evidence of placenta previa. Second, at the time of application of the Willett forceps, the fetal head was the presenting part and no placental tissue was palpated. Apparently, after the Willett forceps tore loose from the fetal head, the forceful and potent uterine contractions completely severed the placenta from its attachment to the uterine wall, thus permitting it to prolapse in front of the head since the presenting part was not engaged. Finally, at the time of delivery, the placenta was lying completely in front of the head, which could not be palpated and the placenta was removed before the internal podalic version and breech extraction could be completed.

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COMPLETE ABRUPTIO PLACENTAE WITH PROLAPSE OF THE PLACENTA

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ABRUPTIO placenta, a complication of the third trimester of pregnancy, occurs about once in two hundred cases according to most authorities. Cosgrove and Conway,¹ in a series of 42,807 live births, found 236 cases, or an incidence of 1:181, while Davis and McGee,² in a review of 40,000 cases, found 164 cases, or an incidence of 1:244. A complete abruptio is an even rarer condition, Davis and McGee² reporting it as occurring in 1:770 cases in their series and DeLee³ reporting it as occurring in 1:500 cases. In very exceptional instances the placenta may become separated from its attachment during the course of labor and be extruded in front of the child. Stander⁴ believes most of the recorded cases were probably instances of placenta previa—although now and again such an accident may occur even when the placenta is inserted normally—so-called “prolapse of the placenta.” True prolapse of the placenta in addition to complete abruptio is a most rare condition, Bland⁵ calling it “extraordinarily uncommon,” while DeLee³ states that only eight cases have been reported in the last twenty years. Kobak, Stein and Daro⁶ who reported two cases in 1941, state the incidence varies from 1:7,000 cases to 1:45,999 cases (the latter from the German literature).

The following is a case report of complete abruptio placenta with prolapse of the placenta and its presentation at the cervical os in front of the fetal head.

D. S., a Negro woman, age 20 years, gravida iv, para i, first reported to the prenatal clinic on June 26, 1947. Her last menstrual period was on March 4, 1947. She gave a history of a normal full-term baby in her first pregnancy, but her second and third pregnancies ended in spontaneous abortion at two months and one and one-half months in August, 1946, and December, 1946, respectively. At this time her Borner-Lukens complement fixation test was negative; smears were negative for gonococci and her Rh factor was positive; hemoglobin was 65 per cent and red cell count was 4,460,000. General physical examination was negative except for slight bilateral lower abdominal tenderness. The patient was started on routine iron, calcium, and vitamin therapy. Her prenatal course was normal until Aug. 14, 1947, when she was admitted to the hospital, twenty-two weeks pregnant, with a threatened miscarriage. At that time, she gave a history of intermittent spotting during her pregnancy, especially at the usual time of the menses, a fact she had not mentioned previously. She was treated successfully and discharged on Aug. 23, 1947. On Sept. 22, 1947, she was admitted to the hospital, twenty-eight weeks pregnant, because of ruptured membranes, but was not in labor. On admission her abdomen was soft, normal uterine resiliency was present and the patient was seeping amniotic fluid. Her blood pressure was 110/70, with hemoglobin 59 per cent and red blood cells 3,960,000. On the night of Sept. 22, 1947, there was slight vaginal spotting and the passage of a small blood clot. On Sept. 23, 1947, vaginal examination revealed no evidence of placental tissue occluding the internal os or on the area immediately adjacent to the internal os. The patient was returned to bed with no bleeding. On the night following examination, patient had a few irregular pains and slight vaginal spotting. In addition to her complaint of pain in the left lower abdomen at this time there was tenderness to palpation in this area and a diagnosis of partial premature separation of the placenta was made and in view of the history of ruptured membranes it was decided to induce labor medically. Patient was given an enema followed by the administration of two doses of Pitocin,



Fig. 1.—Cystic ovary, with corpus luteum and hemorrhagic gestational mass implanted at upper end.

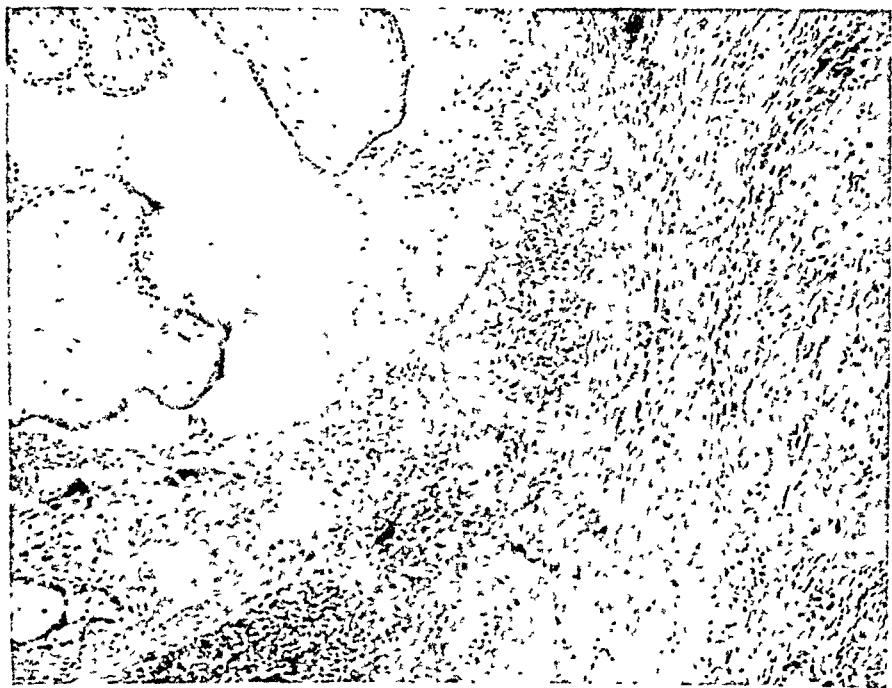


Fig. 2.—Placental villi implanted on ovarian cortex. Lower right field shows corpus luteum. Decidua-like stroma surrounds placental villi in upper left.

OVARIAN PREGNANCY

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WHILE cases of authentic ovarian pregnancy are now being reported with increasing frequency, the condition is still sufficiently unusual to justify single case reports. In 1940, Novak¹ stated that there were about fifty cases which were acceptable, while Curtis,² in 1941, was able to glean sixty authentic cases from the literature. The case presented here is of interest as a typical one of ovarian pregnancy, conforming to all the criteria of Spiegelberg.³

CASE REPORT.—M. G., hospital number 168665. The patient was a 22-year-old white woman who had been married for two years, and was nulliparous. Her menstrual cycle had always been normal and regular in all respects. Her last menstrual period occurred on Nov. 10, 1947, and was in no way unusual. On the evening of Dec. 16, 1947, she began to have mild abdominal pain in both lower quadrants, accompanied by moderate diarrhea, nausea, and vomiting. She was seen by a physician, who found only mild abdominal tenderness without rigidity. The blood pressure was 140/80, temperature 98.4°, F., pulse 90, and respirations 18. A tentative diagnosis of gastroenteritis was made at that time.

On the following morning the pain became increasingly severe, and was now accompanied by severe pain in the right shoulder. The shoulder pain was intensified by any change in position. She was admitted to the Mount Sinai Hospital on Dec. 17, 1947. On admission, the blood pressure was 140/80, temperature 99.2° F., pulse 120, and respirations 32. On physical examination by one of us (B. E. U.), the important findings were marked tenderness in both lower quadrants, worse on the left, as well as rebound tenderness. The patient felt most comfortable while sitting erect in bed. As soon as the back rest was lowered in order to perform a bimanual examination, the abdominal and shoulder pain were markedly aggravated. The senior author has observed the latter finding rather commonly in individuals with ruptured tubal pregnancy. Pelvic examination revealed a uterus which appeared to be normal in size, but the region of the left adnexa was exquisitely tender, making the presence or absence of a mass impossible to determine. There was a definite sensation of fullness in the cul-de-sac with extreme tenderness. The remainder of the physical examination was not remarkable.

A diagnosis of ruptured tubal pregnancy was made and a laparotomy was performed. The peritoneal cavity contained 750 to 1,000 c.c. of clotted and fluid blood. The uterus and right adnexa were normal in every respect. The left Fallopian tube was also entirely normal, but the left ovary consisted of a cystic mass measuring 5.5 by 5.5 cm. A globular hemorrhagic mass, 2 by 2.3 cm., extruded from its distal end. Densely adherent to this mass was an old yellow body. The remainder of the ovary was cystic in character, consisting of a thin-walled cyst, lined by a smooth yellow-brown tissue, and containing a few cubic centimeters of clear yellow fluid. The mass was surgically removed without disturbing the Fallopian tube on the affected side. Recovery of the patient was uneventful, and she was dismissed from the hospital on the sixth postoperative day.

Microscopic examination of the grossly described globular mass showed it to be composed of hemorrhagic exudate, in which were enmeshed innumerable chorionic villi lined by both layers of the trophoblast. This mass was located close to the ovarian cortex; however,

ADENOCARCINOMA OF THE OVARY DIAGNOSED BY VAGINAL SMEAR

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NUMEROUS investigators have reported thousands of cases of cancer of the cervix and uterine body diagnosed when the cytology smears are stained with the Papanicolaou stains.¹⁻⁷

Isbell and others⁸ have reported malignancies of the bladder, urethra, vulva, and Fallopian tube diagnosed by the smear technique; but there appear in the literature no previous cases of cancer of the ovary diagnosed by this method.

Case Report

Mrs. K. P., white, aged 59 years, weight 250 pounds, was first seen on Oct. 4, 1946. She had been bleeding vaginally for past few days. Last menstrual period had been in 1935. She had had a left radical mastectomy on May 31, 1946. The pathologic diagnosis was adenocarcinoma of the breast, Grade II. Following its removal, she had been given a full course of postoperative deep therapy and had had no evidence of metastases. Patient was advised to have a curettage and cervical biopsy, as pelvic examination at this time was negative. This was refused.

She returned again on Feb. 21, 1947, stating that she had had a slight discharge daily since her last visit, but had begun to bleed again on Feb. 20, 1947. Pelvic examination revealed the blood to be coming out of the cervix and, while pelvic examination was unsatisfactory due to a tremendously obese abdomen, the uterus was thought to be enlarged. Vaginal cytology was done according to the Papanicolaou method. Suspicious-looking cells were seen and a curettage was done on March 3, 1947. Microscopic sections showed small fragments of atrophic uterine stroma; there were no glands. Pathologic diagnosis, atrophic endometrium. Examination of the vaginal smears revealed a definite tendency to altered nuclear structure and increase in number of atypical cells. There were present on each of the four stained slides atypical cells exhibiting characteristically hyperchromasia, poor differentiation, and heteroplasia.

On April 4, 1947, biopsy of cervix was done because, when patient was examined on April 3, 1947, there was an ulcerated area at the squamoepithelial junction. Microscopic sections showed a nonstaining mucoid material, through which there were degenerated remnants of outer cervical tissue. The necrotic tissue and mucus were infiltrated with scattered areas of pus and plasma cells. There were no anaplastic cells. Pathologic diagnosis was small fragments of necrotic tissue with pus cell infiltration. There was no evidence of new growth.

The patient continued to have the bloody vaginal discharge off and on. From repeated pelvic examinations, it was definitely felt that the uterus or a possible pelvic mass was enlarging and an exploratory laparotomy was advised. To this the patient finally consented, and this was done on May 20, 1947.

At operation, the patient was found to have bilateral adenocarcinoma of the ovaries extending into the tube. No adherence to other pelvic organs was noted. A bilateral salpingo-oophorectomy, total hysterectomy, and appendectomy were performed. The patient made an uneventful recovery.

The pathologic report by Dr. Lee Howard is as follows:

Gross Appearance.—The appendix appears normal. Body of uterus of average size. On bisection, there is a fibroid in the lateral wall, 1.5 cm. in diameter, and an elongated

it was separated from it by a distinct layer of ovarian parenchyma. The old yellow body described grossly represented a cystic hemorrhagic corpus luteum which was continuous with the previously described cyst.

The findings fulfilled Spiegelberg's criteria.

The additional stipulation added by Norris,⁴ that the tube must show no microscopic evidence of pregnancy, could not be demonstrated here since the tube appeared so definitely normal macroscopically that it was not removed for microscopic study.

In general, two categories of ovarian pregnancy are described. In the first, implantation is intrafollicular, though not necessarily into the follicle from which the ovum is discharged. It is now believed more likely that, after its discharge, the fertilized ovum is implanted in the follicle or corpus luteum. The second, or cortical implantation, is the more frequent mechanism, and we believe that the case reported here falls in the latter category.

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ment. There are scattered areas of degeneration and round-cell infiltration. The ovarian growth has penetrated the cyst wall of both ovaries and will almost certainly invade other tissues of the pelvis and abdominal cavities. The cells of this growth are radiosensitive and deep therapy should be tried.

Six weeks postoperatively the patient was given 3,000 r. in air through 8 abdominal portals and this was repeated six weeks later. Patient has been examined repeatedly at intervals of two to three weeks and so far presents no evidence of metastasis.

On October 20, patient complained of pain in the back and right lower abdomen. Pelvic examination was negative, blood pressure 150/90, weight 244 pounds. Anteroposterior and lateral views of the lumbosacral spine and an anteroposterior view of the pelvis, including both hips, revealed demineralization of the bodies of the lumbar vertebrae with some atrophic and hypertrophic arthritic changes, more marked in the upper lumbar region. There is no evidence of osseous metastasis. Patient was given 300 mg. testosterone propionate in pellets subcutaneously in the right lower abdominal quadrant on Oct. 20, 1947.

Comment

The cells of the vaginal cytology studies and those of the pathologic sections are strikingly similar, indicating that the malignant cells from such sources may be carried into the vagina, either by direct extension or through the fimbriated ends of the tubes.

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fragment or polyp, 4 by 1.5 cm., hanging from the fundus by a narrow pedicle. The left ovary is largely replaced by a cyst, the size of a lemon, in which there is a soft, papillary growth, some of which appears on the outside of the cyst wall. The right ovary is a large mass, the size of a grapefruit, with denuded, papillary projections over the surface. On

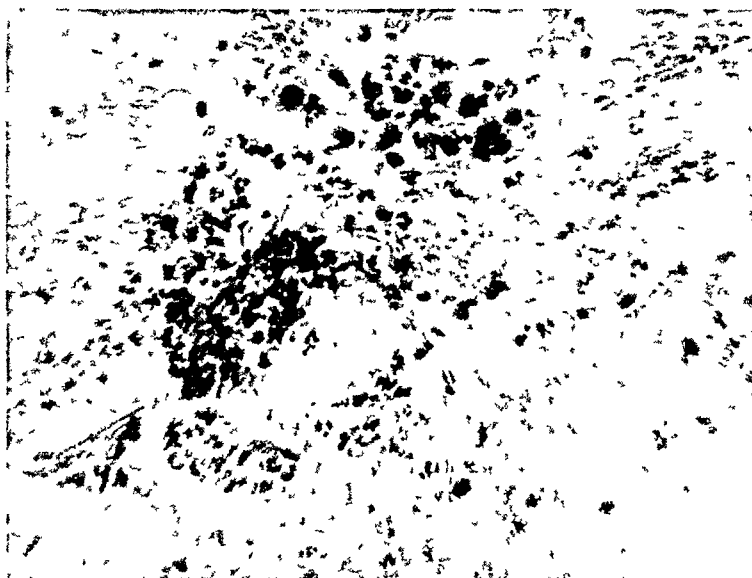


Fig. 1.—Cytology smear. Large malignant cell in center with inclusion bodies and smaller malignant cells surrounding it.

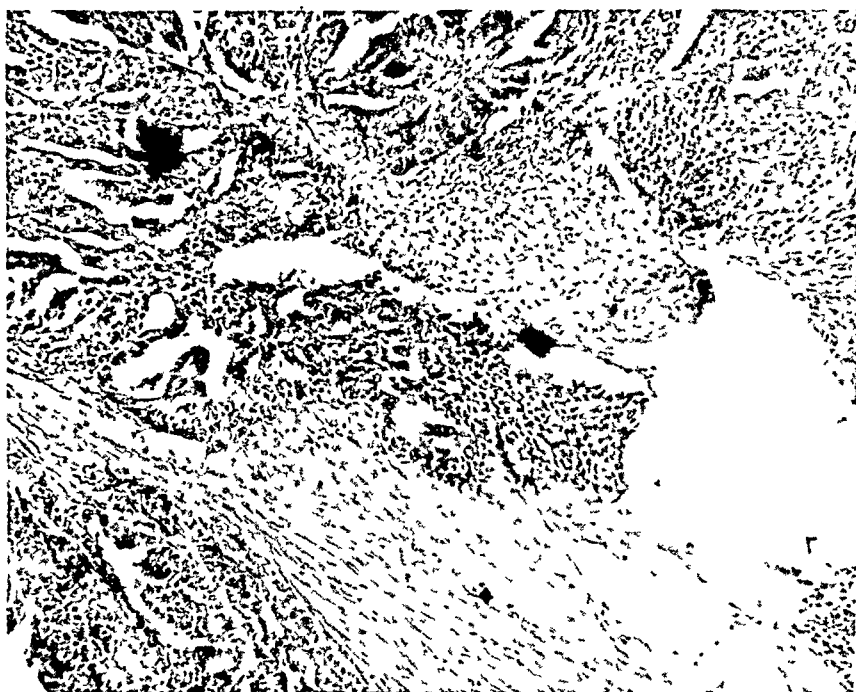


Fig. 2.—Pathologic section of ovaries: adenocarcinoma. Note similarity of the cells on the cytology smear to those on the pathologic slide.

gross section, there is a large, partly macerated growth, 8 cm. in diameter, replacing the ovary, from which two blocks are taken, together with a block from the outside projection, for paraffin sections. Most of the growth is very soft and macerated. Microscopic sections show much the same histology for the three blocks, a cellular growth made up of pale anaplastic cells, some of which have a marked tendency to alveolar and papillary arrange-

strual period, May 26, 1947, she developed a right-sided parotitis, diagnosed as mumps. Following the first skipped period, the patient experienced nausea and vomiting which continued until the time of her next missed period. For this she was treated by diet control and pyridoxine hydrochloride parenterally. A presumptive diagnosis of pregnancy at this time was confirmed by a positive Friedman test. Subsequently, the course of her pregnancy was uneventful.

The total weight gain was 5 pounds, her initial weight being 146 pounds. The expected date of confinement was March 2, 1948. However, spontaneous rupture of the membranes occurred prematurely on Jan. 15, 1948. Active labor began three days later, and she was delivered of a 5 pound, 4 ounce living male child. It was noted that there was a mere crater of skin where the right ear should have been. The external auditory meatus was also absent (Fig. 1). The other ear was apparently normal and there were no other deformities.

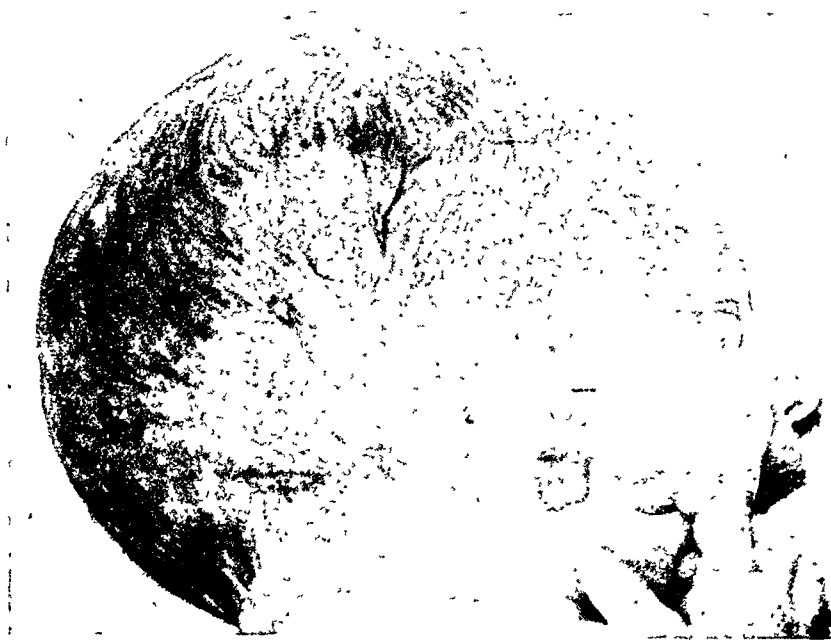


Fig. 1.

Comment.—It is interesting to note that the mumps occurred at a very early stage of embryonic development. The pattern of the plotted basal body temperature of four consecutive cycles observed would indicate that the probable date of conception was on the day of the "ovulation dip." This was on the eleventh day following the onset of her last period and eight days before the parotid enlargement appeared.

Mumps is an infrequent occurrence in the obstetric patient,⁸ and the number of mothers who have had mumps during pregnancy with subsequent fetal abnormalities is indeed small, as noted by published reports. This case affords the inclusion of another instance of mumps occurring in the first trimester of pregnancy with the birth of an infant exhibiting a developmental anomaly.

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CONGENITAL DEFECTS IN THE INFANT FOLLOWING MUMPS DURING PREGNANCY

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INFECTIONOUS virus disease in the gravid woman was shown by Gregg¹ to have an effect upon the fetus. This relationship was observed when rubella was contracted during pregnancy. However, it has been generally known before this that any illness may affect embryonic growth and development. During the pandemic of 1918 it was noted that many gravid women who acquired influenza either died or aborted a dead fetus.² Goodpasture³ indicated by studies on the chick embryo and hen that the embryo is more susceptible to the viruses of vaccinia or herpes simplex, as it produces wide areas of infection in the embryo and causes only a mild lesion in the adult.

Later observations by Swan, Tostevin, and others^{4, 5} corroborated and supplemented Gregg's original work. They also recorded two cases of mumps. In one of these, the mother had mumps at about three and one-half months of her pregnancy. The baby was born with bluish-white bilateral corneal opacities without ciliary injection. However, when the baby was seen twenty months later, the left cornea was clear and the right one was clearing. The second case of mumps occurred late in pregnancy. Interestingly enough the baby had rubella at the same time. No defects were found in this baby. They observed that the "critical period" for the formation of fetal defects was during the first trimester of pregnancy.

More recently, Swan and Tostevin⁶ reported three mothers who had had mumps during pregnancy. Two of these women were infected during their first month of pregnancy, and the third in the seventh month. In the child subsequently born of one of the former, the only abnormality noted was a slight capillary nevus of the right upper eyelid. In the child delivered from the other woman a true anus was absent and the large intestine terminated in the labium majus. There were no abnormalities except for a head-circumference which was slightly below normal in the baby born from the third mother who contracted mumps late in pregnancy.

The case reported herein is one in which mumps had appeared shortly after conception, with the subsequent delivery of a premature living child exhibiting developmental defects of the right ear.

M. F., a 31-year-old white female was a gravida ii, para 0. She was married two years and had had two spontaneous abortions; the first one soon after marriage and the other at the end of the first year. The pregnancies were of short duration, terminating two weeks and three and one-half weeks following skipped periods, respectively. Curettage was performed following the latter. Recovery was without sequelae.

Menses were regular, recurring every twenty-six to twenty-seven days, with a moderate flow of four to five days' duration. Basal body temperatures were recorded, and the monthly cycles were plotted.⁷ Four consecutive periods were observed. The temperature curves were of a biphasic pattern, with "ovulation dip" occurring on day eleven of the cycle.

The patient's serology (Mazzini Reaction) was negative; blood group was AB, and she was Rh positive. The blood count showed 12.5 Gm. hemoglobin, 9,650 white blood cells, and 4,510,000 red blood cells. The differential count was normal. Blood cholesterol was 258 mg. per cent, and basal metabolism rate was a plus 6 per cent. The husband's serology (Mazzini Reaction) was negative, blood group A, and Rh positive. The semen specimen was considered satisfactory, the sperm count being 71,000,000 per cubic centimeters. There were 80 per cent motile sperm, 85 per cent were normal, 10 per cent were major abnormalities, and 5 per cent were minor abnormalities.

Conception occurred in the fifth cycle. This was estimated to have taken origin on day eleven, June 5, 1947. On June 13, 1947, nineteen days following the onset of her last men-

VAGINAL CALCULUS NOT DUE TO URINARY LEAKAGE OR FOREIGN BODY*

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B. F., 34 years old, white, unmarried, was seen in my office for the first time on May 26, 1947, for a "checkup" examination because of mild dysmenorrhea and inability to use vaginal menstrual tampons. Past history was noncontributory. The patient had had the usual childhood diseases and pneumonia in infancy. Menstruation had begun at 12, and had been regular, every 21 to 25 days, lasting 4 to 5 days, with a moderate flow. Moderate to severe abdominal cramps usually accompanied the periods. The patient stated that she usually had a slight white mucoid vaginal discharge. Frequent headaches were associated with the menses. Review of systems was within normal limits except for occasional urgency on urination. No history could be obtained of possible introduction of a foreign body into the vagina. General physical examination was within normal limits and catheterized urinalysis was negative throughout. Adequate pelvic examination could not be done because of an almost imperforate hymen through which it was barely possible to pass a uterine sound a distance of about 1.5 cm. The external genitals appeared normal and on rectal examination the uterus and adnexa could not be outlined with any degree of exactitude. Because of the findings, admission to the hospital for hymenectomy was advised.

The patient was admitted to Methodist Hospital and, on June 7, 1947, under sodium Pentothal anesthesia, operation was performed. By means of gentle instrumental and digital manipulation, the hymenal opening was gradually enlarged. However, about two centimeters behind the vaginal introitus, the vagina was found to be almost completely obliterated by a stony, hard mass which was everywhere densely adherent to the vaginal walls. By means of careful probing, a small passageway was found between the stone and the anterior vaginal wall. It was not possible to remove the mass intact since it was wedged so firmly in the vaginal tissues. Finally, the stone was grasped and removed piecemeal with Kocher clamps. There was a marked stenosis of the vagina at about the midportion and the stone had developed in this region. It was particularly fixed to the posterior vaginal wall. There was no connection with the bladder. Bleeding was profuse during the operation and sutures were necessary to control the bleeding at the hymenal site and the midportion of the vagina. The cervix appeared normal and the uterus and adnexa were normal to palpation. At the completion of the operation, a moderately firm vaginal packing was put in place. Despite the obvious trauma of the operative manipulation, the patient withstood the surgical procedure very well. However, at 12:00 midnight on the day of the operation the patient developed chills and fever and her temperature rose to 103.4° F. The vaginal packing was removed at this time and penicillin therapy was instituted. The temperature came down to normal in forty-eight hours and the patient was discharged in good condition. Since discharge from the hospital I have examined her on a number of occasions and when last seen on Dec. 5, 1947, she had an adequate, but snug vagina with slight contracture of the hourglass type in the midportion. She was symptom free, but had employed daily vaginal tampons for three months after operation in order to maintain an adequate vaginal tube.

The pathological report as submitted by Dr. Russell Richardson is as follows: Specimen consists of two calcified pieces five and six millimeters in diameter and some fine "sand." All are dark brown in color.

*Presented before the Obstetrical Society of Philadelphia, Feb. 5, 1948.

ERRONEOUS PROGNOSIS BASED ON INCORRECT INTERPRETATION OF THE HYSTEROSALPINGOGRAPHY FILM*

ALEXANDER GABRIELIANZ, M.D., CHICAGO, ILL.

MRS. N. S. D., aged 31 years, by profession a ballerina, consulted me because of sterility. She had been married five years and had never become pregnant. Menstruation began at 13 years, regular, four-week type, three to four days in duration. She had occasional dysmenorrhea of a few hours' duration on the first day. Her past history was negative, both medically and surgically. She is subject to nervous tension and unbalanced emotions.

Clinical examination revealed no pathologic findings. On examination, the uterus was in normal anteflexion, slightly enlarged, of normal consistency, symmetrical, freely movable, not tender. The adnexa were not palpable.

The examination of the husband's seminal fluid performed within one hour after intercourse showed the spermatozoa in abundance, vigorously motile, with normal length of tails and normally shaped heads.

Following this examination a hysterosalpingography was performed on the wife on Dec. 27, 1946. The visualization of the internal female organs was preferred to insufflation due to the patient's occupation. Often insufflation leads to excruciating pains in the shoulders and thus invalids the patient. 9 c.c. of Lipiodol were used. After injection of 8 c.c. the patient complained of pain in the uterine region. One more cubic centimeter was added before taking the pictures. 1 c.c. of iodized oil is sufficient to fill up the tubes and pass through the fimbriated end of the tubes. The spill is moderate in amount and gives the possibility of correct interpretation.

Five minutes later the second x-ray picture was taken. The last picture was taken after twenty-four hours. The first picture showed the right tube patent, the upper third of the left tube was visualized. On the second picture there was slight visualization in the proximal end of the right tube; visualization in the left tube was the same. The last picture showed no evidence of oil in the pelvis.

From the pictures I felt that pregnancy was unlikely. Because of the findings on hysterosalpingography, I told her that contraceptives would not be necessary.

The patient left the city but reported by letter later that she had had her last menstrual period on Jan. 27, 1947 and that for the first two months she danced without realizing that she was pregnant, feeling well all the time. I was later informed that the patient was delivered of a baby girl on November 7.

The conclusion is that iodized oil in the left tube passed into the abdominal cavity, perhaps straightening out the kink or relieving some other obstruction in the tube.

25 EAST WASHINGTON STREET.

*Presented before the Chicago Gynecological Society, Nov. 21, 1947.

Summary

Vaginal calculus is a rare condition. The cases that have been mentioned in the literature were thought to be caused by vaginal cysts, calcified fibroid tumors, or urinary leakage into the vagina. One case (Reeb³) was thought to be due to calcification of mucous cells.

A case of vaginal calculus is reported apparently caused by stagnation of the menstrual flow due to an almost imperforate hymen and an apparent congenital stenosis at the midportion of the vagina.

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The material removed at operation was submitted to Dr. Abraham Cantarow for qualitative analysis and he reported findings positive for: (1) fibrin, (2) hemoglobin, (3) calcium carbonate, (4) phosphate; and negative for (1) ammonia and (2) urate. He stated that the absence of the latter constituents was very good evidence against the possibility that the material was of urinary origin. He stated that the material probably originated in constituents of the blood and vaginal or uterine secretions.

Masson and Appell¹ in 1934 reviewed the literature on vaginal calculi and were able to discover twenty-two authentic cases of vaginal calculi, including their own two cases from the Mayo Clinic.

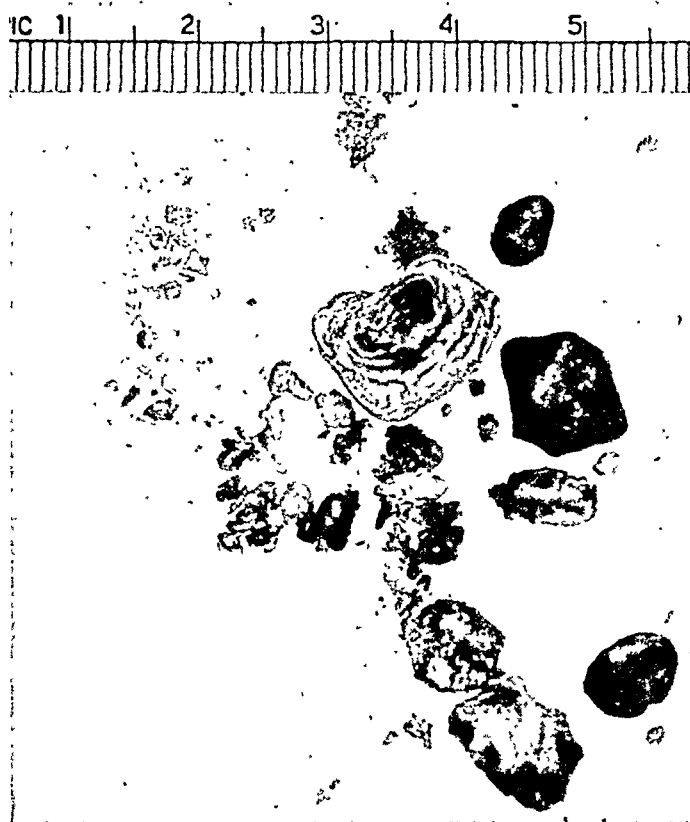


Fig. 1.—Photograph of calculus after removal.

Mohler² has maintained that persistent cases of vaginal discharge, of apparently unknown etiology, may occasionally be due to vaginal micturition. One case (reported by Reeb³) was of rather indefinite etiology. A seventy-year-old patient had been treated by dilatation, curettage, and intrauterine radium application. Two years later, a large vaginal calculus was found. It was not a calcified tumor histologically and it was not thought to be urinary in origin because of the absence of fistula. It may have arisen from calcification of mucous cells.

Since 1934, several other cases of vaginal calculi have been reported, all associated with congenital or acquired vaginal stricture and the occurrence of urinary leakage into the vagina through a fistula or as a result of urinary incontinence. Stansfield,⁴ in 1942, reported a vaginal calculus associated with a vesicovaginal fistula and complicating parturition. He makes the observation in this paper that vaginal calculi were more frequently mentioned in the older literature since the operation of colpocleisis was then in vogue for the relief of vesicovaginal fistulas.

The stone described in this communication apparently arose from the precipitation of salts of the menstrual flow due to stagnation induced by the congenitally small hymenal opening and the apparent congenital vaginal stenosis. I believe we may safely rule out urinary, foreign body, or tumor origin.

was normal to auscultation. There was a well-healed right paramedian scar which was exquisitely tender to palpation, with rebound tenderness referred to it from the left side. No hernias were present. Pelvic examination could not be done because of a virginal introitus. Rectal examination revealed a nontender retroverted uterus, the manipulation of which produced severe lower abdominal pain. The left vault was negative, although the right vault was thought to contain a slightly enlarged, very tender ovary.

At this time a diagnosis of *mittelschmerz* was made, with possibility of endometriosis or a twisted right ovarian cyst kept in mind.

Laboratory Work.—Catheterized urine was found to be essentially negative. Red blood count was 4,230,000, and the hemoglobin was 12.5 grams. The white blood count was 6,400 with a normal differential. The sedimentation rate was 5 mm. in sixty minutes.

Hospital Course.—About three hours after admission, repeated examination revealed moderate lower abdominal muscle spasm, but was otherwise as on admission. Twenty-one hours later there was found to be marked spasticity of the entire lower abdomen, and increased peristalsis to auscultation. Because of these additional findings, an exploratory laparotomy was done twenty-seven hours after admission, and the following findings were noted: the omentum was held by three fingerlike adhesions to the under surface of the old appendectomy scar. These were considered to be inconsequential, and in no way related to the presenting symptoms. The right ovary on its superior-anterior-medial surface showed a classical corpus hemorrhagica, with a prominent stigma actively oozing serosanguineous fluid. The left ovary on its supero-posterior-medial aspect presented a similar but slightly smaller stigma, which also was actively oozing bloody material. The largest diameters of the ruptured follicles were 0.75 cm. and 0.50 cm., respectively. In the cul-de-sac was found approximately 125 c.c. of fresh blood-stained fluid. Except for generalized hyperemia of the pelvis, the remaining findings were essentially negative. The abdomen was closed in layers, and the patient was returned to her room in good condition. The postoperative course was smooth, except for a small wound hematoma, which granulated in well.

Discussion

This case presents a problem in the differential diagnosis of the acute abdomen in the female. In spite of a typical history consistent with the diagnosis of *mittelschmerz*, more serious pathology could not be ruled out without laparotomy. The progressive involvement of both lower quadrants made an additional diagnosis likely.

Subsequent to surgery, the patient's threshold to pain was found to be fairly low, which may have contributed to the initial, complicated, clinical picture.

Statements relative to the fact that bilateral follicular rupture is thought to occur quite frequently have been found in the literature, but there have been no recorded observations of this condition.

Summary

A case of bilateral follicular rupture is described which is thought to be the first such case to be seen at operation and recorded in the literature.

BILATERAL FOLLICULAR RUPTURE

Report of a Case Seen at Operation*

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WALTER G. LEONARD, LT. J.G. (M. C.) U.S.N.R., CHELSEA, MASS.

(From the Dependents' Department, U. S. Naval Hospital)

THE following is a report of a case of bilateral follicular rupture which was seen at operation. A careful review of the literature fails to reveal any record of previous observation of this phenomenon.

Miss K. J. M., a 27-year-old, single, Navy Nurse from this hospital, was admitted on Dec. 18, 1947, from duty, because of acute lower abdominal pain of fifteen hours' duration. The present illness began three months before admission with a continuous "heavy feeling" in the lower abdomen. This occurred exactly two weeks after the onset of her previous menstrual period and eleven days prior to the next period. This symptom felt similar to an impending period which she knew was not due at that time. There was slight nausea, but no vomiting, and all the discomfort subsided in three days. Two months prior to entrance, at the exact, same, midmenstrual time, a second similar, but not disabling, attack occurred. This likewise subsided in three days. One month before admission, at the same midmenstrual time, a third attack occurred, which was more severe, and caused her to vomit. The pain at this time lasted five days. Fifteen hours prior to admission, while shopping, she was seized with a very sudden attack of excruciating, lower abdominal pain, most severe in the right lower quadrant. This sharp pain was soon superseded by a dull aching sensation. Severe nausea and vomiting ensued and the pain was only partially affected by $\frac{1}{2}$ grain of codeine. This attack occurred on Dec. 17, 1947, fourteen days after the onset of the previous catamenia, which was normal. Bowels and kidney function were normal. She was admitted to the hospital on the next day.

Menstrual History.—Menstruation began at thirteen years of age, and was regular in cycles of twenty-five days, the periods lasting seven days until the present illness, then lasting three days, with less copious flow. There were occasional clots and moderate dysmenorrhea during the first day of flow. There was no leucorrhea. The last flow began on Dec. 3, 1947, and was normal except for two small clots.

Past History.—At 10 years of age, the patient had a tonsillectomy and right mastoidectomy. At thirteen years of age she had jaundice with gall stones proved by x-ray, for which no operation was performed. At 20 years of age an appendectomy was performed for ruptured appendix, but no drain was left in place, and she recovered in two weeks. For six months following this surgery, her periods were irregular. Also, at 20 years, she was hospitalized with a diagnosis of rheumatic fever, with joint pains, epistaxis, chills, fever, and hemorrhagic purpura, the latter of which she has had intermittently since. At 24 years of age she had an operation performed for correction of an internal strabismus of the left eye. At that time, a tentative diagnosis of brain tumor was considered, but eventually ruled out.

Family History.—The family history was essentially negative except that her father died at 39 years of rheumatic heart disease.

Physical Examination.—A well-developed, well-nourished, white female, in acute lower abdominal distress was lying on her right side, with her thighs flexed on her abdomen, and moving only with exceeding caution for fear of accentuating the pain. The abdomen was soft, with moderate involuntary muscle spasm, particularly in the left lower quadrant. No masses or fluid were made out. The liver, spleen, and kidneys were not palpable. Peristalsis

*The opinions published are those of the authors, and in no way reflect the opinion of the U. S. Naval Medical Corps.

He found negative smears in 263 women and positive smears in 51 cases, an unusually high incidence of 16.2 per cent. He does not mention whether this series represents a special series of cases.

Among the 51 positive cases were 35 cervical carcinomas, all confirmed by biopsies. In 33 cases of this subgroup the indication for biopsy was made by the prebiopsy smear, providing thus a 5.72 per cent error. Seven of nine adenocarcinomas of the endometrium suspected by smear were confirmed by curettage, an error of 12.23 per cent. In addition, the author found perfect agreement of the smear reports in two vulval carcinomas, one clitoral carcinoma, and one case of uterine sarcoma. The over-all percentage of error for the entire series was 2.22 per cent, an unusually low figure, or 7 cases from the series of 314 cases. When divided into "false positives" and "false negatives" (8.9 per cent) the final corrected percentage was 5.59 per cent. Among the cervical carcinomas were 12 cases of Grade I lesions (League of Nations classification).

Schtirbu concludes the Papanicolaou prebiopsy procedure represents as valuable a contribution as the biopsy, periodic pelvic examinations, and colposcopic studies toward earlier detection of genital malignancy and the ultimate reduction of mortality rates in uterine cancer.

CLAIR E. FOLSOME.

Kullander, S.: Chorionepithelioma Treated With Stilbestrol, *The Lancet*, page 944, June 19, 1948.

Nineteen months after expulsion of a hydatid mole, a 20-year-old multipara was found to have chorionepithelioma, with two deposits in an enlarged uterus, theca lutein cysts of the ovaries, and small metastatic deposits in the lungs. After removal of the internal genitals, she was given a total of 3,400 mg. of stilbestrol by mouth and 18,500 mg. parenterally, until her death five months later. The possible beneficial effects of this treatment were shown by: (a) clinical improvement on initiating therapy, (b) reduction of gonadotrope titer following the initiation or large increase of stilbestrol dosage, (c) reduction in size of vaginal and lung metastases on increasing the dosage, and (d) rapid increase in gonadotrope titer and enlargement of vaginal metastasis on temporarily stopping stilbestrol administration.

IRVING L. FRANK.

Pund, Edgar R., Dick, Fred, Jr., and Cardwell, E. S. Jr.: The Pathology of Early Carcinoma of the Cervix. The Status of Preinvasive Cancer, *South. M. J.* 41: 711, Aug., 1948.

Incipient preinvasive carcinoma of the cervix has come into the realm of diagnostic possibility since the introduction of the Papanicolaou smear for cytologic study. There were 86 cases of preinvasive carcinoma, 28 of which were discovered before hysterectomy, and 69 uteri in which routine pathologic examination inadvertently made the diagnosis. Diagnosis depends entirely upon cytologic detail, namely: nuclear hyperchromatism, increase in the nuclear-cytoplasmic ratio, variations in nuclear size and absence of polarity. The cells in preinvasive carcinoma resemble in all respects the cells of invasive carcinoma. The incidence runs between 1.5 per cent and 3.9 per cent in large numbers of uteri studied following hysterectomy for various causes.

Preinvasive carcinoma is seen in a disproportionate number of pregnant uteri. Basal cell proliferation normally occurring in pregnancy may make differential diagnosis difficult.

Preinvasive carcinoma seems to remain preinvasive for an average of six years. It is possible that some may never progress to the invasive stage. However, the diagnosis demands immediate hysterectomy because such treatment should be followed by 100 per cent cure. A discussion of this paper by Dr. Emil Novak suggests that there is not unanimity of opinion regarding the pathologic criteria for the diagnosis of preinvasive carcinoma.

WILLIAM BICKERS.

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Tietze, Christopher: Abortion as a Cause of Death, *Am. J. Pub. Health* 38: No. 10, Oct., 1948.

The author presents a comparative study of mortality from abortion which shows a striking decline of such deaths in the years 1927 to 1945. The drop in mortality rate in septic abortion has been much faster than that with nonseptic abortion; this supports the view that increased efficiency of treatment of infections with chemotherapy and antibiotics is reflecting itself in this field.

This presentation also offers data showing regional and racial differences in these mortality rates. In general, mortality from abortion has been higher in the Negro than in the white population. It is interesting to note that among white women mortality from abortion is lowest in New England, the Middle Atlantic States, and on the Pacific Coast, but does not vary much according to the size of the community.

This paper concludes with a presentation of comparative international abortion mortality rates. S. B. GUSBERG.

Delfs, E., and Jones, G. E. Seegar: Some Aspects of Habitual Abortion, *South. M. J.* 41: 809, Sept., 1948.

Habitual abortion is the term reserved for the patient who has suffered three consecutive, spontaneous abortions. The incidence of habitual abortion is about 0.4 per cent of all pregnancies. The most common etiologic factor is hypothyroidism, having been encountered in 72 per cent of the 39 patients with habitual abortion and was the sole factor in 44 per cent. Pregnanadiol excretion values were below normal in 28 per cent. Low chorionic gonadotropin excretion was found in six patients, all of whom aborted. Specific treatment was administered on the basis of laboratory diagnosis, thyroid being given to the hypothyroid; progesterone, to those with low pregnanadiol excretion. Chorionic gonadotropin was withheld from those showing a low excretion of this hormone because it is believed that this indicates a morbid or dead fetus. Successful termination of the pregnancy occurred in 67.4 per cent of 33 patients studied, whereas the expectation of spontaneous recovery in this group is something below 27 per cent. WILLIAM BICKERS.

Cancer, Malignancies

Schtirbu, Isaac: Colpocytology in the Diagnosis of Uterine Cancer, *Obst. y ginec. latino-am.* 6: 201-210, May, 1948.

The author, reporting from the Gynecology Service at Rawson Hospital in Buenos Aires, gives an analysis of his experiences with the Papanicolaou method in the pre-biopsy method for the detection of early carcinoma of the genital tract in 314 patients.

Endometriosis

McGuff, P.: Endometriosis as a Cause of Obstruction of the Intestine, Proc. Staff Meet., Mayo Clin. 23: 215, 1948.

In sixteen cases of intestinal obstruction caused by endometriosis at the Mayo Clinic, the average age was thirty-nine years; the ages ranged from thirty-one to fifty-four years. Ten of the patients were married; two were separated from their husbands; four had never married. There had been only three pregnancies, with two living children, in the group of married women. A pelvic operation had been done in nine of these cases; eight patients complained of dysmenorrhea. In nine patients the menstrual cycle was regular; in four patients, irregular; two patients had had a hysterectomy done, and one had amenorrhea. Four patients had menorrhagia, and two, metrorrhagia. The average duration of the menstrual symptoms in these cases was six and a half years; and the average duration of the symptoms of intestinal obstruction was 4.8 years. The symptoms of intestinal obstruction included abdominal pain in all cases; constipation at the time of the menstrual period in thirteen cases; abdominal distention in ten cases; obstipation in ten cases; rectal pain, diarrhea, and vomiting in five cases each; and blood in the stools in three cases. On examination, abdominal tenderness was found in seven cases and an abdominal mass in three cases. Complete obstruction of the sigmoid had developed in four cases; partial obstruction developed in six cases, in the sigmoid in three cases, in the rectosigmoid in two cases and in the distal part of the ileum in one case. Chronic intermittent obstruction of low grade occurred in the remaining six cases, involving the sigmoid in three cases, the distal part of the ileum in two cases, and the rectosigmoid in one case. Sigmoidoscopic examination was done in twelve cases, and showed the lesion in nine of these cases; roentgenograms of the colon showed the lesion in nine of eleven cases. A definite diagnosis was not made before operation in six cases; in seven cases a diagnosis of endometriosis as the cause of intestinal obstruction was made; in two cases a diagnosis of carcinoma was made; and in one case, a diagnosis of appendicitis with ileus.

The possibility of endometriosis as a cause of intestinal obstruction should be kept in mind in women thirty to fifty years of age. A history of acquired dysmenorrhea, abnormalities of menstrual periodicity, sterility, rectal or pelvic pain, the presence of associated uterine fibroids (in eight cases in this series) or ovarian cysts (in ten cases), and a long history of progressive intestinal obstruction, especially with exacerbations at the menstrual periods, are suggestive of endometriosis as the cause of the obstruction. The presence of a firm tumor in the rectovaginal septum or of tender palpable nodules also suggests endometriosis. If sigmoidoscopic examination shows an extrarectal mass and intact mucosa, or if the roentgenogram shows a long inconstant filling defect, with sharp, regular border and intact mucosa, such findings are a valuable adjunct for the diagnosis of endometriosis when the lesion is in the lower bowel. When the obstruction is in the ileum, the symptoms are less characteristic and preoperative diagnosis is more difficult.

The treatment of intestinal obstruction due to endometriosis is surgical. If the diagnosis of endometriosis can be made preoperatively in cases of colonic obstruction, resection of the bowel is not necessary in most cases, but temporary colostomy is done if indicated, and panhysterectomy. If the obstruction is in the ileum, ileal resection is indicated and the degree of associated pelvic endometriosis determines whether oophorectomy and panhysterectomy are indicated. In younger women, if obstruction of the ileum or sigmoid is caused by a discrete endometrioma, and the pelvic organs are sufficiently normal to give a reasonable chance of pregnancy, a radical operation on the bowel is indicated, and a conservative operation on the ovaries. In older women, a radical pelvic operation and a conservative operation on the bowel are indicated. In all cases in which a clinical diagnosis of endometriosis causing obstruction of the bowel is made, a biopsy and immediate frozen section should be done at operation in order to rule out carcinoma. In the series of sixteen cases reported, there was no operative mortality, and the prognosis is considered to be excellent.

HARVEY B. MATTHEWS.

Endocrinology

Herschberg, A. D., Frommel, E., and Piquet, J.: Serum Cholinesterase and Sex Glands, *Annales d'Endocrinologie* 9: 117-130, 1948.

The authors find that the sexual hormones exercise a positive influence upon the activity of serum cholinesterase (pseudo-cholinesterase). These activities, especially those concerned with estrogen, are indirect. The pituitary gonadotropins are inhibited by cholinesterase in vivo and in vitro. In clinical practice the excess estrogenic and androgenic activity elevates the serum cholinesterase and in insufficient amounts of the estrogen and androgen the values are decreased.

The authors conclude that the basic lessons found in their studies reside in two theories: (1) the vasodilator action of estrogen is due to an overproduction of acetylcholine locally which becomes in some manner a regulator of estrogenic activity, and (2) the estrogenic receptors characterize themselves by the presence in their tissues of some pseudo-cholinesterase and the acetylcholine production is increased by the estrogenic effect. CLAIR E. FOLSOME.

Varangot, J., and Labatut, M.: The Use of the Quantitative Vaginal Smear in the Standardization of Estrogens in the Woman, *Gynéc. et obst.* 47: 540-543, 1948.

The measurement of activity of an estrogenic substance in the adult woman is often difficult. To ascertain the minimal effective dose from a minimal quantity of estrogenic substance one is forced to rely upon endometrial biopsies of oophorectomized women. This is obviously inconvenient. The authors therefore evaluated the quantitative study of the vaginal smear as a possible alternative method. Using the Papanicolaou procedure and stains as he outlined it in *Science*, April, 1942, the authors studied vaginal smears in a woman who had had a surgical menopause five years before to learn that 92 per cent of the cells were from the deeper layers. They use as a formula the observations on the menopausal case studied for five years: basal cells 07; prickly cells 87; pyknotic cells 08; granular cells 00 and anuclear cells 00. The first two groups fall into the deep group (Dr. Papanicolaou's C 1 and C 2 or K 1 and K 2—the basal and lower parabasal layers) and the upper three groups are in the superficial layer (Dr. Papanicolaou's C 3, C 4, and C 5 or K 3, K 4, and K 5—the upper parabasal, intermediate or navicular, and superficial or squamous). By application of this study to 25 ovariectomized women, the average formula :02-90/08-00-00: for the smear was found.

In a group of women treated with 50 mg. of estradiol benzoate pellets the average formula was found to be :00-15/60-25-00: In other words, 85 per cent of the cells in the smear were from the third or fourth layer of the vaginal epithelial strata. The writers conclude that when a smear contains more than 70 per cent of the basal or lower basal cells from the deep layer there is an absence of estrogen while a smear showing less than 30 per cent of cells from the deep layer has adequate estrogens. The physiological variations will fall between these two extremes, thus the quantitative vaginal smear does provide in the woman a sensitive guide to evaluating compounds with estrogenic activity. It is more accurate than clinical signs and is much simpler than repeated endometrial biopsies.

CLAIR E. FOLSOME.

Gori, R. M., and Di Guglielmo, L.: Complications Produced by Implantation of Estrogenic Pellets, *Anales del Instituto de Maternidad y Asistencia Social* 7: 46-51, 1945.

"Professor U. Fernandez"

The authors present three cases in which the implantation of 30.0 mg. and 50.0 mg. pellets of diethylstilbestrol dipropionate caused untoward symptoms. One patient complained of mastodynia for several days; on two occasions there occurred prolonged metrorrhagias, the endometrium in one case presenting the picture of cystic glandular hyperplasia. The authors conclude this mode of therapy has little place in gynecologic practice save for the isolated menopausal case which does not respond to other therapy. CLAIR E. FOLSOME.

For endocervicitis or ectocervicitis of the Grades I or II and ectoendocervicitis of Grade I, a superficial conization will suffice. He terms this procedure *preconization* and stresses the avoidance of radical treatment because of the obvious complications; in other words, he permits distal drainage with minimal fibrous tissue change. For endocervicitis or ectocervicitis Grade III and ectoendocervicitis, Grades II or III, he advised excision of the cervix. Ten illustrations are included.

CLAIR E. FOLSOME.

Laborit, M. H.: Uterine Hemorrhages and Atropine, Gynec. et obst. 46: 585-588, 1947.

The author, reasoning that the vasomotor function of the uterus is primarily under the vagal sympathetic dominance and that the cholinergic vasodilators and adrenergic vasoconstrictors influence uterine vessels, feels that there is no reason we should not attribute the same influence on innervation of uterine vessels to control of uterine muscle tonicity. He treated eight cases of functional uterine bleeding with subcutaneous atropine, 1.0 mg. per day for one to two days. In six of these cases he was able to bring about cessation of bleeding. He concludes that this drug should receive more study as a possible non-endocrine method to control functional bleeding. Douay in his discussion points out that Laborit has good reasoning that atropine is not without dangers and we should withhold conclusions pending further studies.

CLAIR E. FOLSOME.

Netter, Albert: A Study Upon the Cervico-Uterine Temperature, Presse Méd. 56: 506-507, July 17, 1948.

The author had reported in a previous study (Annales d'Endocrinologie 8: 194-199, 1947) that there existed a definite difference between rectal and cervical temperatures. In normal women the cervical temperatures were found to average 0.5 to 0.7° C. higher than the rectal temperatures. The cervicouterine temperature showed variations in the course of the menstrual cycle. While more elevated than the basal rectal temperature patterns, the outline was similar in character except for a rise with subsequent fall of 0.3 to 0.5° C. at ovulation time followed by a secondary rise 0.3 to 0.4° C. It was observed, too, there was an abrupt drop of 0.5 to 0.6° C. about two days before the onset of the next menstruation.

In menopausal patients the author notes a consistently lower cervicouterine temperature as compared to rectal temperature, an average of 0.1 to 0.4° C. The author attributes the rise or fall of the cervicouterine temperature to estrogenic levels and carries out corollary observations of cervicouterine temperatures with vaginal smears. The administration of 2.0 to 5.0 mg. of diethylstilbestrol caused increased cervicouterine temperatures in eighteen of twenty cases so studied.

He concludes that the cervical temperature, without doubt, is a test of estrogenic function but that other multiple factors preclude its complete reliability as a single diagnostic method.

CLAIRE E. FOLSOME.

Di Fonzo, N. O.: Endocervical Flora in Pregnancy, Bol. Soc. de obst. y ginec. de Buenos Aires 26: 548-553, Nov. 13, 1947.

Di Fonzo studied the flora in vaginal and endocervical mucus of sixty pregnant women. He describes elaborate precautions used in taking bacteriological specimens. The endocervix, habitually sterile, can harbor certain discrete microbiological flora without harm to the function of the mucous plug. The acidophilic bacilli and enterococci were most frequently encountered in the vagina and the endocervix. There was found no appreciable difference in bacterial flora in the second or third trimesters. The author concludes that his study stresses the need for sterile conditions attending intrapartum care. A full bacterial spectrum is not included.

CLAIR E. FOLSOME.

Gynecology

Kermorgant, Y.: On the Subject of Genital pH, *Presse Méd.* 56: 381, May 29, 1948.

The author, studying the pH of the cervical and vaginal mucus in obese women, records his detail from 300 observations. All determinations were taken after coital abstinence or vaginal instillations for at least 24 hours prior to examination. Mucus was taken with a capillary pipette and determinations were made with a colorimeter. The mucus becomes more acid as one approaches the introitus from the distal end of the canal. Kermorgant found a pH of 7.0 at time of ovulation in cervical mucus but he noted that the cervical alkalinity is greater with increased estrogen activity. When the pH shifts more to the acid side one must consider decreased follicular activity. This correlation of alkalinity pH of cervical mucus increase to hyperestrination and a more acid pH of hypoestrination may be useful in clinical application.

CLAIR E. FOLSOME.

Gallo, Delfino: Biomechanics in Gynecology, *Ginec. y obst. de Mexico* 3: 181-195, June, 1948.

Gallo, of Guadalajara, reviews from the literature several methods appertaining to evaluation of the possible relation of posture in the erect position in women to the position of genital organs and symptomatic gynecic disorders. He includes in these methods: (1) simple inspection; (2) silhouette graphic studies; (3) measurement of the depth of the lumbar curve; (4) the direct measurement of pelvic inclination; (5) tracings of the spinal curvatures, and (6) roentgenographic studies. The spinal curvature tracings were taken directly by using a unique but simply devised pantograph.

Among the 154 women studied, only forty could be classified as having normal or good posture. Another 113 women exhibited defective posture of the so-called "gorilla" type in different degrees, while one case was classified as "kangaroo" type posture. In summary, he noted a marked tendency toward a change in position of the genital organs in those cases with defective posture. Thirteen figures accompany the article.

CLAIR E. FOLSOME.

Monteiro, Aurelio: Histological Basis for the Treatment of Chronic Cervicitis, *An. brasil. de gynec.* 26: 23-26, July, 1948.

The author believes the histological pattern of the chronically infected cervix uteri should constitute the choice of method of treatment for this condition. He develops an interesting pathological classification of cervical infections, briefly, (1) endocervicitis; (2) ectocervicitis, and (3) ectoendocervicitis. Each of these three is broken down into three smaller categories. Endocervicitis of Grade I is limited to localized inflammatory changes about the racemose glands with moderate foriglandular round-cell infiltration; Grade II, when the inflammatory process involves deeper tissues, and Grade III, when inflammatory changes are found with hyperplastic squamous metaplasia of endocervical cells, else atypical columnar-cell hyperplasia of endocervical cells.

Ectocervicitis, Grade I, is the true or pseudoerosion with superficial round-cell infiltration; Grade II, erosion or pseudoerosion associated with Nabothian cysts or chronically lacerated cervix, and Grade III, hyperactive basal cells of squamous portio with or without proliferative atypical cornified superficial layers.

Ectoendocervicitis, Grade I, indicates coexistence of Grades I or II of endocervicitis with ectocervicitis; Grade II includes endocervicitis I or II with ectocervicitis I or II while Grade III of the ectoendocervicitis group indicates an association of Grades III of both the endocervicitis and ectocervicitis groups.

Monteiro states that any treatment should be preceded by biopsy to rule out carcinoma and to classify the extension and type of pathologic process so more effective treatment may be done.

Newborn

Shelton, Kost, E., Varden, Arthur E., and Mark, Jerome S.: Experimental Use of Testosterone Compounds in Premature Infants, *J. Clin. Endocrinol.*, October, 1947.

In a previous communication, Shelton and Varden showed that the administration of methyl testosterone apparently increased the survival rate of premature infants weighing less than 2,000 Gm. The present study strongly suggests that there is a marked diminution in the initial weight loss of prematures if these infants are given 5 mg. of methyl testosterone orally, or 4 mg. of testosterone propionate intramuscularly daily. The effectiveness of the testosterone regime is further demonstrated by administering it to one each of four sets of twins with very satisfactory results in so far as maintenance of weight and weight gain is concerned. It is stated that the administration of testosterone causes a decline in urinary nitrogen with no increase in fecal nitrogen and, from this, it is deduced that this nitrogen retention, with the concomitant decrease in sodium, potassium, and chloride urinary excretion, aids in tissue building.

Finally, the authors ridicule any suggestion that the administration of testosterone to infants for a few weeks might interfere with future growth. HERBERT J. SIMON.

Gruenwald, Peter: Mental Deficiency of Prenatal Origin: A Challenge to Preventive Medicine, *Am. J. M. Sc.* 214, 605, Dec., 1947.

This paper presents a thorough review of the literature to date on the prenatal causes of mental deficiency, blindness and deaf-mutism. The author submits a classification which includes fetal infection, under which he places syphilis, toxoplasmosis, and rubella: fetal deficiency of iodine or oxygen, also fetal pituitary deficiency; group incompatibility; malformations of unknown origin; and, finally, birth injury resulting from mechanical causes and anoxia.

The problem of eugenics is briefly touched upon. The various causes listed above are then discussed in some detail.

The author concludes that, with the information now available to physicians, it may no longer be said that the antenatal causes of mental deficiency are beyond control. He urges that the most extravagant research program in this field may be lower in cost than the public maintenance of persons whose mental deficiency is of preventable prenatal origin.

A very extensive bibliography, covering all recent contributions to this subject is included. HERBERT J. SIMON.

Richdorf, L. F., and Cady, L. H.: Peritonitis in the Newborn of Intrauterine Origin, *Journal-Lancet*, page 188, May, 1948.

The authors report a case of peritonitis and intestinal obstruction in an infant during his neonatal period. ~~No bacteriological studies are presented but a postmortem examination is described, which suggests that this peritonitis originated during intrauterine life.~~ The authors postulate a relationship between this disorder in the infant and an episode of "intestinal flu" in the mother, approximately two weeks before delivery. S. B. GUSBERG.

Heilig, W. R., Tudor, R. B., Smith, T., and Platou, E. S.: Report of 26 Cases of Erythroblastosis Fetalis and Survey of the Literature, *The Journal-Lancet*, page 222, June, 1948.

A review of the advancing knowledge of Rh factors and erythroblastosis fetalis is presented. The authors then describe their experience with twenty-six cases and demonstrate the efficiency of the exchange transfusion and its superiority over the older method of periodic transfusion. The recovery of erythroblastotic infants whose mothers had previously borne sick babies who succumbed to this disease emphasizes the importance of this therapy.

S. B. GUSBERG.

Miscellaneous

Stuart, Harold C.: Effects of Protein Deficiency on the Pregnant Woman and Fetus and on the Infant and Child, New England J. Med., 1948.

This paper is a review of the current knowledge concerning protein nutrition of the mother, the fetus, and the infant. The first part of the paper deals with the marked increase in protein requirement of the woman during the last half of her pregnancy. The usually recommended diet of 85 Gm. of protein a day is considered adequate. The negative nitrogen balance of the puerperium, especially as it relates to lactation, is discussed and the reserve nitrogen stored during pregnancy is suggested as the protective mechanism against this loss. However, the work of both Burke and Williams is quoted to show that only about 13 per cent of pregnant patients take the advised amount of protein.

The relationship of protein intake to lactation is discussed and a diet containing 2 Gm. of protein per kg. of body weight is recommended for successful lactation.

The relationship of a low-protein diet to amenorrhea, relative sterility, toxemia of pregnancy, various anemias, abortion, and infant mortality rates are discussed.

A correlation between protein intake, prematurity, and infant weight is suggested.

The effect of low-protein diet on the growth and development of infants is discussed and much of the recent literature cited. The following table of recommended protein intake for children of various ages is quoted from Levine.

SUBJECTS	AGE	PROTEIN PER
		KG. OF BODY WEIGHT (GM.)
Premature infants	1 week to 1 month	6.0-4.4
Premature infants	1 to 3 months	4.4-3.3
Full-term infants	2 days to 3 months	4.4-3.3
All infants	4 months to 1 year	4.0-3.0
Toddlers	1 through 3 years	4.2-2.9
Preschool children	4 through 6 years	3.3-2.5
School children	7 through 9 years	2.6-2.1
School children	10 through 12 years	2.2-1.8
Youths, female	13 through 15 years	1.8-1.5
Youths, male	13 through 15 years	2.0-1.7
Youths, female	16 through 20 years	1.6-1.4
Youths, male	16 through 20 years	2.1-1.7

L. M. HELLMAN.

Gillman, J., Gilbert, C., and Gillman, T.: Rupture of the Uterus of Nutritional Origin—An Experimental Study in the Albino Rat, South African J. M. Sc. 12: 153, Dec., 1947.

Rats raised on special diets consisting largely of corn and soya bean meals, skim milk, linseed oil, and minerals, developed spontaneous rupture of the uterus in six of twenty-five pregnant animals (24 per cent incidence). The unspecified dietary defect did not prevent sexual maturity and impregnation, but growth rate was reduced, and one animal showed mild rickets. Mechanical causes for uterine rupture were absent, since the animals did not show pelvic deformities or oversize embryos, and since rupture occurred in late pregnancy before the onset of labor.

Uterine rupture is one-sixth as common in European women as in Chinese or in the South African Negro women. In these latter groups, poor obstetric care and malnutrition are the factors in common. Chronic malnutrition may lead to an imperfect development of uterine connective tissue or to degenerative changes in the myometrium, and thus reduce the strength of the uterine wall. Such a situation would explain ruptures occurring before the stress of labor, ruptures in labor without apparent disproportion, and the predisposition to rupture in the obese, metabolically abnormal woman.

IRVING L. FRANK.

Tompkins, W. T.: *The Clinical Significance of Nutritional Deficiencies in Pregnancy*, Bull. New York Acad. Med., page 376, June, 1948.

The nutritional studies of the Philadelphia Lying-In Hospital are presented in this review, with a description of the optimum diet recommended in pregnancy and the disorders resulting from dietary abnormalities. Common dietary indiscretions are discussed and the importance of proper nutritional education and supervision emphasized.

The author presents clinical data supporting his contention that subclinical nutritional deficiencies are very common in pregnancy. He emphasizes the need for vitamin supplements and also stresses correlation between adequate protein intake and the hemoglobin level.

The data presented indicate considerable superiority of a group supervised nutritionally over a nonsupervised group with respect to the incidence of pre-eclamptic toxemia, premature delivery, and infant mortality. It is concluded that inadequate nutrition plays a major role in the etiology of these pregnancy abnormalities.

S. B. GUSBERG.

Puerperium

Ping y Roig, P.: *Uterine Rupture in the Puerperium*, Anales del Instituto Corachan 1: 13-17, 1948.

The author, chief of Obstetrical Service at the Corachan Institute in Barcelona, reports an unusual case of rupture of the uterus during the puerperium. The patient, a 39-year-old gravida vi, entered the clinic after previous outside attempts to induce labor with oxytocic agents. The uterus was in a state of tetany. A cherry-sized fibroid was noted during the examination. It was part interstitial and part submucous in location. The patient was delivered ultimately, with aid of forceps, of a normal infant. She remained in good condition for the first twenty-four hours after delivery. Suddenly she went into deep shock. Examination revealed a uterine rupture at site extending from the sclerotic tissue surrounding the small fibroid. The author reasons that the suckling of the newborn baby evoked a uterine-mammary reflex which extended the incipient uterine tear beyond the muscle to the serosa. Conservative medical care, antibiotics, and simple repair permitted discharge of the patient on her thirteenth postpartum day.

CLAIR E. FOLSOME.

Leon, Juan: *Intravaginal Sulfonamide Therapy During and After Delivery, Prophylaxis in Puerperal Sepsis*, Anales del Servicio de Obstetricia del Hospital Cosme Argerich 1: 95-103, Dec., 1947.

The author describes his results from the instillation of various kinds of sulfonamide powders into the vaginas of women before and after delivery. He used sulfanilamide, paraminobenzene sulfonamide, sulfathiazole, and sulfadiazine in 494 women at the onset of labor and two hours after the third stage.

The group of patients with normal temperatures was greater (90.8 per cent) than in women not having this treatment (77.5 per cent). The series treated with mercurochrome instillations found 77.7 per cent with normal temperatures as compared to 87.7 per cent treated with oral sulfonamide therapy. Subnormal temperatures were found to be present in only 8.0 per cent of the cases, while a minimum of 1.2 per cent of the total series evinced low-grade febrile responses. The article is well documented with eight tables.

CLAIR E. FOLSOME.

Trillat, Paul, and Dumont, Martial: *Paralysis of the External Popliteal Branch of the Sciatic Nerve in Puerperium*, Gynec. et obst. 46: 413-419, 1947.

The authors, from Lyon, review the findings in six women, all recently delivered, who developed in the postpartum period transient paralyses of the external popliteal

Complications of Pregnancy

Mendoza, J. T.: Incarceration of Six-Month Gravid Uterus, *Philippine J. Surg.*, page 58, March-April, 1948.

A young primigravida admitted in active labor during the sixth month of pregnancy was found to have the pelvic basin completely filled by the uterine fundus, which further rose to a height of 12 cm. suprapubically. The cervix was at the upper pubic border, and could not be felt vaginally. During uterine contractions, the perineum became tense, and the anterior rectal and posterior vaginal mucosae bulged through their respective orifices. There was associated urinary retention with "paradoxical incontinence."

A 25 cm. fetus was delivered by cesarean section, the patient recovering. Incarceration in this case may have been due to a flat pelvis with an overhanging sacral promontory (conjugata vera was 8.5 cm.), which prevented the usually spontaneous ascent of a retrodisplaced gravid uterus.

IRVING L. FRANK.

Chesley, R. F., and Annitto, J. E.: Evaluation of Molybdenized Ferrous Sulfate in the Treatment of Hypochromic Anemia of Pregnancy, *Bull. Margaret Hague Maternity Hosp.*, page 68, Sept., 1948.

This well-controlled study of hypochromic anemia in pregnancy reveals an incidence of 6.6 per cent in a group of patients chiefly in the second trimester.

The presented data show a considerably more efficient hematologic response in those patients treated with a combination of molybdenum sesquioxide and ferrous sulfate over that group treated with ferrous sulfate alone. A smaller group treated with iron in combination with liver-stomach concentrate or folic acid demonstrated no increase in benefit. The authors also present lesser data suggesting that the molybdenized ferrous sulfate preparation was better tolerated, for the group of patients treated with this medication showed no significant gastrointestinal intolerance.

This presentation concludes that such a ferrous sulfate combination is more efficient than the conventional therapy of hypochromic anemia in pregnancy. It states that the precise role of molybdenum in potentiating the iron is, as yet, unknown.

S. B. GUSBERG.

Chesley, L. C.: Does Eclampsyogenic Toxemia Cause Chronic Hypertension? *Bull. Margaret Hague Maternity Hosp.*, page 81, Sept., 1948.

The author critically evaluates the literature concerning the relation of the duration of pre-eclampsyogenic toxemia to subsequent hypertension and concurs in the majority opinion which favors such a correlation. He challenges the evidence used by some to label the pre-eclampsyogenic syndrome in patients developing later chronic hypertension as that of latent essential hypertension. He cites the work of his own group which demonstrated a fairly constant relationship between prolonged duration of toxemia and later chronic hypertension whether or not the pregnancy was interrupted or the patient permitted to go into labor; he also presents data which fail to show a late increase in chronic hypertension in post-toxemic patients such as one might expect if these patients were simply latent hypertensives.

S. B. GUSBERG.

Winston, B. J.: Hydatidiform Mole With Eclampsia Occurring in the Fourth Month of Pregnancy, *Illinois M. J.*, page 221, April, 1948.

This report adds another case of hydatid mole with eclampsia to the literature of this subject. This 19-year-old primipara developed convulsions and anuria during the fourth month of her pregnancy and died within twenty-four hours without emerging from coma. Unfortunately, postmortem examination was limited to the abdominal organs.

S. B. GUSBERG.

Sheehan, H. L.: Postpartum Necrosis of the Anterior Pituitary, Irish J. M. Sc., No. 270, June, 1948.

In previous papers published in 1937 and 1940, the author reported nineteen examples of the early stage of postpartum necrosis of the anterior pituitary. At that time there were only twenty-three previous cases reported in the literature. Since 1940, only fourteen additional cases have been reported. In this paper twenty-two cases found at the Glasgow Royal Maternity Hospital between 1940 and 1946 are reported in some detail. As in the previous papers, no pituitary necrosis has been found if the patient died less than twelve hours postpartum. At about twelve to fifteen hours there are definite cellular alterations in the pituitary glands, and by twenty-four to thirty-six hours the changes are easily recognizable. Patients dying within six to eight hours after delivery, of conditions which would be expected to give rise to pituitary necrosis, show a peculiar edematous appearance of the pituitary gland. The changes are not, however, striking enough to make a definite pathological diagnosis. The lesion is always dependent on thrombosis of parts of the vascular supply to the gland, and is invariably associated with severe circulatory collapse either as a result of hemorrhage and/or shock at the time of delivery. In 92 deliveries where death was not associated with circulatory collapse, no pituitary necrosis was found. The obstetrical causes of pituitary necrosis are those which would be expected to provide circulatory collapse. Postpartum hemorrhage with retained placenta was the most prominent, followed by placenta previa and accidental hemorrhage. Rupture of the uterus, inversion of the uterus, prolonged labor, and eclamptic shock have also played a role in the etiology of this condition. There are no recorded cases of pituitary necrosis occurring in the presence of a continuing pregnancy. So far as is known, the circulatory collapse giving rise to pituitary necrosis is always associated with the end of pregnancy. Patients with large areas of pituitary necrosis show certain physiological disturbances in the puerperium which may be related to the pituitary gland. The breasts fail to enlarge, and lactation is inhibited. In a few cases, rather low blood sugar has been found. Two cases are reported in which patients with rather marked pituitary necrosis showed large outputs of urine. Failure of the pubic hair to return or very sparse growth has also been reported. The author estimates that in the 1930s one-eighth of the total maternal deaths would show some degree of pituitary necrosis. He feels that this would be reduced in the 1940s by improved obstetrics and more efficient treatment of those cases showing hemorrhages. The reduction in the total number of maternal deaths through the use of penicillin and sulfonamides will also reduce the absolute number of cases of early necrosis of the pituitary gland found at autopsy. The author estimates that evidence of severe chronic hypopituitarism in patients who have survived severe circulatory collapse during delivery ranges in the region of 1 in 2,500 adult women. L. M. HELLMAN.

Jeffcoate, T. N. A.: Post Partum Necrosis of the Pituitary, Irish J. M. Sc., No. 270, p. 256, June, 1948.

This author feels that clinical hypopituitarism is more rare than Sheehan has indicated. The author gives a short and inconclusive discussion of the treatment of patients with Simmonds' disease with the known existing hormones. Some good results are reported with gonadotrophins, androgens, and estrogens. L. M. HELLMAN.

Cunningham, J. F.: Obstetrical Shock and Pituitary Ischemia, Irish J. M. Sc., No. 270, p. 268, June, 1948.

The author states that early treatment of pituitary necrosis is essential in saving the life of the patient. A patient who has sustained hemorrhage and shock should be carefully observed during the early puerperium. The earliest symptoms of pituitary necrosis are slow recovery, lethargy, low blood pressure, low blood sugar, mental confusion, and refusal of food. Treatment consists primarily of prevention of hemorrhage and shock. In the early

branch of the sciatic nerve (common peroneal nerve division). The duration of labor in four cases was the following respective number of hours: 44 hours, 17 hours, 26 hours, 17 hours; and in two instances the injury followed rapid delivery. Three were delivered by forceps. Four were localized to the right lower extremity and two to the left side. All but one of the patients complained of violent sacroiliac pain in the last stages of labor, but the transient paralysis appeared at the eleventh, fourth, fifth, tenth, eighth, and the first day after delivery. The paralyzes cleared in the following number of days: fifteen days in three cases; twenty to twenty-one days in two cases; and in six months in one case. In the latter case there was an atrophy of 2.0 cm. of the left leg with steppage gait. Treatment consisted of B complex, diathermy heat, and small doses of strychnine salts. CLAIR E. FOLSOME.

Leon, Juan: Maternal Mortality in the Province of Buenos Aires, *Archivos de la Clinica Obstetrica y Ginecologica* "Eliseo Canton" 3: 196-215, May, 1944.

The author, former Director General of the Health Department of the Province of Buenos Aires, analyzes the maternal mortality for the years 1929 to 1943, inclusive. There were 1,040,271 deliveries. In this fifteen-year period there were 2,513 maternal deaths, an incidence of 2.38 per cent. There was a gradual decline in the maternal mortality over the fifteen-year period, viz.: 1929 (2.82 per cent); 1934 (3.17 per cent); 1937 (2.94 per cent); 1939 (2.00 per cent); 1942 (1.72 per cent); and 1943 (1.80 per cent). In Peru, in 1940, the maternal mortality was calculated as 6.7 per cent.

In the seven years, 1937 to 1943, the number of deliveries in the hospitals varied from 19.0 to 26.0 per cent of all deliveries. The frequency of operative interference varied from a low of 2.5 per cent in 1942 to 8.1 per cent in 1937 in those cases hospitalized. Abortion, as a sole cause of maternal death, accounted for 8.6 per cent of the total deaths. Eclampsia deaths accounted for 0.9 per cent of the total figure. The principal causes of maternal death were the infectious or septic processes. Eight tables are included. CLAIR E. FOLSOME.

Sheets, Maurice V.: Usual and Unusual Findings in the Cervix Uteri at Time of Repair Immediately Following Delivery, *West. J. Surg.* 56: 317, June, 1948.

Small pieces of tissue from the cervix removed immediately following delivery were examined microscopically in 200 consecutive postpartum patients. Decidual reaction occurred in 40 per cent of the specimens. Proliferation of squamous cells marginally invading columnar epithelium, a finding known as epidermization was found in 12 per cent. Metaplasia appeared in glandular epithelium or in a continuation of normal squamous epithelium sufficiently often to be considered normal in pregnancy. Intraepithelial preinvasive cancer occurred only where invasive cancer was found elsewhere in the specimen. Clinically unsuspected, grossly nondiscernible cancer occurred twice in a series of 200 patients and it is interesting to note that clinical symptoms did not appear in these two patients during six months of observation following delivery. These cases would seem to substantiate observations made on rats that pregnancy delays tissue invasion by malignant cells.

WILLIAM BICKERS.

Newman, H. F.: Ligation of the Inferior Vena Cava and Ovarian Veins for Infected Abortion, *Am. J. Surg.*, page 746, May, 1948.

This is a case report of a patient with septic abortion and multiple pulmonary emboli treated by ligation of the inferior vena cava and the ovarian veins with eventual recovery. The postoperative course was marked by wound disruption and mechanical obstruction of the bowel but was free of further pulmonary complications. No follow-up evaluation of her vascular or pelvic status is presented. S. B. GUSBERG.

Correspondence

Estrogens in Management of Eclampsia

To the Editor:

As the proponent of the use of estrogens in the management of realized pre-eclampsia and eclampsia,¹⁻⁴ I was greatly interested in the paper by Dr. O. W. Smith appearing in the November issue of the JOURNAL. It has been a tedious task to compile all my data on this subject, and this letter is accordingly a very tardy comment on the toxemic section of her valuable article.

The writer has used virtually nothing but estrogens in the management of late toxemia cases since 1936. His experience in these twelve years does not quite bear out the statement of Dr. Smith that "stilbestrol administration alone as a definitive measure in late pregnancy toxemia is fruitless." Indeed, the fact that practically nothing else need be used in the management of 92 consecutive unselected pre-eclampsies and 19 consecutive unselected convulsive eclampsies, all private patients, would indicate that such a remark falls somewhat short of the mark. The details of the management of many of these patients have been recorded in the papers listed above.

In the 92 pre-eclampsies there were no maternal deaths, but in the 19 eclampsies the maternal mortality was 10.5 per cent. The fetal mortality in the two groups was respectively 3.4 and 16 per cent. The average birth weight of the children in these two groups, excluding twins, triplets, macerates, and deaths undelivered was, for pre-eclampsies, males, 7 pounds, 8 ounces, and females, 6 pounds, 14 ounces; for eclampsies, males, 5 pounds, 11 ounces, and females, 4 pounds, 2 ounces. Of the whole series only 48 per cent of the pre-eclampsies were induced or sectioned and only 72 per cent of the eclampsies.

In the last 26 consecutive unselected pre-eclampsies so treated, only one patient convulsed (seen in consultation 24 hours beforehand), although the antenatal diastolic pressures (fourth phase) of six of these women at one time or another equalled or exceeded 120. Of these 26 women, 17 had only a trace of albuminuria or less as labor began, and only 14 were induced or delivered by section. The average duration of these pregnancies was 39.5 weeks. Of the twelve examined six weeks post partum, seven had normal blood pressures and no albuminuria. Indeed, the average time post partum required for any albuminuria to decrease to a trace or less was twenty-four hours!

The effect of large doses of intramuscular estradiol benzoate on convulsive patients is of great interest. Prevention of further convulsions is almost invariably achieved after seven hours have elapsed, restoration of orientation and decrease of edema ensue, urine excretion is maintained, and there is as well a *very* rapid decrease of albuminuria after delivery in most instances.

Our estrogen dosage is by no means as large as Smith and Smith have advised. Rarely have we given more than 8 mg. of stilbestrol per day, and even of late have in only a few instances exceeded 15 mg. per day. That these doses are of significant value is best indicated by the fact that one often finds relief of all the toxic signs and symptoms on 15 mg., where 10 mg. have failed, or on 8 mg. where 5 mg. have failed.

It is difficult to believe, after experiences repeated so often, year after year, that the huge dosage of the Smiths is either physiological or needed. Our own empirical evidence suggests that the daily dosage in pre-eclampsies should more nearly approximate the average daily excretion near term, since obviously only partial replacement is necessary. In convulsing cases, a much higher level of dosage is demanded; however, our present routine calls for 100,000 I.U. of estradiol benzoate injected intramuscularly every four hours until all danger of fits has passed, usually thirty-six hours post partum.

puerperium, if the condition is suspected, carbohydrates, glucose, and saline are necessary. The author states that adrenal cortical extract may have some beneficial results.

L. M. HELLMAN.

Kaltreider, D. Frank, and Dixon, D. McClelland: A Study of 710 Complete Lacerations Following Central Episiotomy, *South. M. J.* 41: 814, Sept., 1948.

Great is the difference among obstetricians as to the relative merits of central and mediolateral episiotomy. A comparative study of the two episiotomy techniques is presented. The disadvantage of central episiotomy is thought by some to be the higher incidence of third-degree laceration which it invites. In two of the Baltimore hospitals, rectal laceration followed in 4.49 per cent of a large series delivered with central episiotomy. As one would expect, 92 per cent of these occurred in primigravidas. The forceps operation following prolonged labor with consequent edema and congestion of the tissue favored extension of the central episiotomy into the rectum. The author wisely refrains from comment upon the relation of the pelvic outlet diameter to the incidence of third-degree laceration because measurements in this series were made by many different physicians. Rectovaginal fistula occurred only once in the entire series. Weighed against these obvious disadvantages of central episiotomy are many advantages which have led the authors to adopt it as a routine.

The central incision increases the soft tissue anterior-posterior diameter; vaginal lacerations are rare; there is less tension on the suture line following repair; pain is minimal; repair is more rapidly accomplished, and with more accurate anatomical approximation. The technique for repair and aftercare is given in some detail. It is probably not advisable to use central episiotomy in the occiput posterior position, but in the great majority of deliveries it is the operation of choice when employed by the trained and experienced obstetrician.

WILLIAM BICKERS.

Venereal Diseases

Rosenthal, Theodore, and Kerchner, George: Venereal Disease in Prostitutes, *Am. J. Syph., Gonorr. & Ven. Dis.*, 1948.

A study of women arrested in New York City on prostitutional charges from 1936 to 1946 has revealed a decrease in latent syphilis from 1936 to 1944 but a subsequent increase in the two succeeding years. There has also been an increase in the incidence of gonorrhea during the decade but this may be due to better methods of study rather than to a real increase. The greatest percentage of infectious venereal disease was found in girls under 20 years of age.

L. M. HELLMAN.

Goodwin, M. S., and Farber, M. S.: The Necessity for Treatment of Pregnant Syphilitic Women During Early Pregnancy, *Am. J. Syph., Gonorr. & Ven. Dis.* 32: 409, Sept., 1948.

This excellent study was set up to evaluate the necessity for retreatment of syphilitics in pregnancy. The authors briefly review the literature of this subject and cite several reported series in which treatment was withheld and normal infants were obtained. They present, thereafter, a moderately large series of patients from their own clinic who had received prior adequate treatment with metal chemotherapy and a small group treated with penicillin, permitted to undertake another pregnancy without further treatment. In no case was a syphilitic infant obtained. There was no increase in fetal mortality over that of children of non-syphilitic women.

The workers conclude that it is safe to permit a syphilitic patient to undertake pregnancy without further treatment, if her previous antisyphilitic therapy has been adequate, if she is free of clinical signs of active syphilitic infection, and if she is seronegative or, if positive, in low titer only.

S. B. GUSBERG.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Ludwig Emge. *Secretary*, Norman Miller, Ann Arbor, Mich. Next meeting, May, 1949, Hot Springs, Va.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, James R. Bloss, Huntington, W. Va. *Secretary*, Leroy A. Calkins, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 7-9, 1949.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Earl C. Sage, Omaha, Neb. *Secretary-Treasurer*, John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Oklahoma City, Okla., Nov. 3, 4, and 5, 1949, Municipal Auditorium.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, C. J. Andrews, Norfolk, Va. *Secretary*, E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Next meeting, Feb. 9, 10, and 11, 1950, Hotel Roanoke, Roanoke, Va.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, William F. Mengert, Dallas, Texas. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.
- New York Obstetrical Society.** (1863) *President*, Albert H. Aldridge. *Secretary*, Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Carl Bachman. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, Herbert E. Schmitz. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, Henry S. Acken, Jr. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Edward Friedman. *Secretary*, Lester J. Bossert, 2404 Auburn Ave., Cincinnati 19, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James Hodgkiss. *Secretary*, Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.
- Obstetrical Society of Boston.** (1861) *President*, M. Fletcher Eades. *Secretary*, H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.
- Washington Gynecological Society.** (1933) *President*, Henry L. Darner. *Secretary*, John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.
- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Woodard D. Beacham. *Secretary*, Harry Meyer, 3439 Prytania St., New Orleans, La. Meetings held October, November, January, March, and May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

Estrogenic therapy for toxemia has little to offer the average practicing obstetrician if it is useless in the last four weeks of gestation when most of his toxic problems become accentuated, and if it is valueless in established cases. But if it is prophylactic one could expect it to be therapeutic in some modification or other, which agrees with our observation.

Any physician can quickly test the validity of our contention for himself, and will then be more optimistic about it, perhaps, than the writer of your leading article for November.

EVAN V. SHUTE, F.R.C.S.(C).

The Shute Institute,
London, Ontario,
January 3, 1949.

References

1. Shute, E. V.: *Endocrinology* 21: 594, 1937.
2. Shute, E. V., and Barrie, M. M. O.: *AM. J. OBST. & GYNEC.* 40: 1003, 1940.
3. Shute, E. V.: *Am. J. Surg.* 59: 478, 1943.
4. Shute, E. V.: In preparation.

Item

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathology examinations (Part II) for all candidates will be conducted at Chicago, Illinois, by the entire Board from Sunday, May 8, through Saturday, May 14, 1949. The Hotel Shoreland in Chicago will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Shoreland.

Candidates for re-examination in Part II must make written application to the Secretary's office not later than April 1, 1949.

Candidates in military or Naval Service are requested to keep the Secretary's office informed of any change in address.

Applications are now being received for the 1950 examinations. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.
1015 HIGHLAND BUILDING
PITTSBURGH 6, PENNSYLVANIA.

- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Harley E. Anderson. *Secretary*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Gerald Rogers. *Secretary-Treasurer*, Arthur A. Hellbaum, 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, Robert E. Faulkner. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Herschel Murphy. *Secretary*, Benjamin Daversa, Spring Lake, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, Frank C. Spencer. *Secretary-Treasurer*, H. McLeod Patterson, 202 King Kalakaua Bldg., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Duncan R. Neilson. *Secretary-Treasurer*, David M. Baker, 520 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, A. D. Cook. *Secretary*, L. O. Frederick, 413 Third National Bldg., Dayton 2, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Moses Cohen. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held third Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, Walter Simmons. *Secretary*, Richard H. Street, Jr., The Street Clinic, Vicksburg, Miss. Meetings held semiannually.
- Florida Obstetrical and Gynecological Society.** *President*, Charles J. Collins. *Secretary*, Dorothy D. Brame, Orlando, Fla. Next annual meeting, Belleair, April 10, 1949.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, Manly E. Hutchinson. *Secretary*, J. Decherd Guess, 200 E. North Street, Greenville, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
- El Paso Gynecological Society.** (1948) *President*, F. A. Snidow. *Secretary-Treasurer*, C. C. Stapp, 800 Montana Street, El Paso, Texas.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, W. O. Johnson. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.

- St. Louis Gynecological Society.** (1924) *President*, A. N. Arneson. *Secretary*, Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Julius McIver. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex. Annual meeting, Dallas, Texas, September, 1949.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Obstetricians and Gynecologists.** (1938) *President*, Chester E. Clark. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, Gilbert F. Douglas. *Secretary*, Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Donald J. Thorp. *Secretary-Treasurer*, Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, Lyman W. Mason. *Secretary-Treasurer*, Jack M. Simmons, Jr., 638 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Henry A. Sincock. *Secretary-Treasurer*, Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, P. L. Martin. *Secretary*, Albert P. Kimball, 233 "A" St., San Diego, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, H. A. Wheeler, Grand Forks. *Secretary*, C. B. Darner, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Walter McMann. *Secretary-Treasurer*, L. L. Shamburger, State Health Department, Richmond, Va. Next meeting not announced.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Wayne Brehm. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Charles W. Frank. *Secretary*, Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino, Everett. *Secretary*, C. Wendell Knudson, Medical and Dental Bldg., Seattle, Wash. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Joseph G. Webster. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, L. G. Baldwin. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, J. Ross Vant. *Secretary*, J. O. Baker, Edmonton, Alberta. Annual meeting, June 18 to 22, 1949, at Jasper Park Lodge, Jasper National Parks.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, George A. Palmer. *Secretary-Treasurer*, Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.
- Minnesota Society of Obstetrics and Gynecology.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.

be repeated here. It suffices to mention that, since the introduction of the term by Bandl in 1875, there is no single subject in the field of obstetrics which has been the source of as huge a literature. It was not until the concept of the isthmus uteri was introduced by Aschoff in 1905 that tacit agreement was reached as to the origin and boundaries of the lower uterine segment. The thesis of Aschoff was accepted in its entirety, and extended by Stieve. From this basis has developed our present understanding of the lower uterine segment.

I. The Present Concept

The classical concept of the lower uterine segment is difficult to summarize in specific terms since the structure is so variously interpreted. However, it is possible to outline certain fundamental features upon which most are agreed. According to present understanding, the lower uterine segment takes its origin specifically from the isthmus uteri of Aschoff. It will be recalled that the isthmus of the nonpregnant uterus, according to original definition, is a structure from 6 to 10 mm. long interpolated between cervix and corpus, bounded superiorly by the constriction in the lumen known as the anatomic internal os, and inferiorly by the point of transition from endocervical to isthmic type of mucosa, the histologic internal os. Stieve and Aschoff have reported lengthening of this segment in early pregnancy,² and dilatation down to the level of the histologic internal os so that the isthmic wall comes to form, together with the corpus, part of the wall of the ovum chamber. The site of the obliterated anatomic internal os is said to be marked by a ledge or thickening of the musculature which has been designated as the physiologic retraction ring.⁵ This ring remains until the termination of pregnancy, dividing the uterine cavity into two portions which are designated as the upper uterine segment and the lower uterine segment, respectively. Upon the basis of evidence both from frozen sections at term and examination of the uterus at the time of elective cesarean section, it has been shown that the region of the lower segment is thinner than that of the upper, and that the transition between the two is often abrupt. It is shown further that during labor there is progressive thinning of the lower uterine segment in contradistinction to the thickening which occurs in the upper, and that, in the presence of neglected obstructed labor, uterine rupture occurs through this attenuated lower segment. Because of the latter finding, together with other evidence which is not clear to the writers, the lower uterine segment is believed to be passive in labor, in contrast to the upper portion which performs the active work of parturition. The thinning of the lower pole is assumed to occur as the result of longitudinal stretching of this segment, the evidence for this being the gradual elevation of the physiologic retraction ring on the abdomen as the corpus thickens.

Certain descriptive terms have been coined to clarify the precise changes in the muscle fibers during these happenings.⁵ Though slow of acceptance, they or some similar terms are essential to an adequate understanding of the uterine adjustments of labor. The term *brachystasis* was introduced to describe the changes in the corpus, consisting of a progressive, ratchetlike thickening in this segment with successive pains. It connotes a cycle of contraction of a single muscle fiber, during which the fiber first contracts, and then relaxes to a shorter length than before the contraction but at this shorter length it manifests the same tension as it did prior to contraction. By a series of such contractions the fiber becomes progressively shorter, but in its relaxed phase, despite this shortening, its relaxed tension is not altered. By envisioning the entire musculature of the upper segment contracting in this wise, one can readily understand the progressive thickening and shortening which occurs in this segment. The converse of *brachystasis* is *mechystasis*, which connotes an interval fixation at greater

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THE LOWER UTERINE SEGMENT*

Its Derivation and Physiologic Behavior

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IN ALL natural phenomena the principles from which we start, like the conclusions which we reach, embody only relative truths. The experimenter's stumbling block, then, consists in thinking that he knows what he does not know, and in taking for absolute, truths that are only relative."¹ In the case of the lower uterine segment, one must recognize that he deals only with working hypotheses rather than established facts, and that as new information is made available the hypothesis must be altered to conform with it.

In a previous article,² it was shown that the so-called "isthmus uteri" of the nonpregnant uterus is a variable segment whose boundaries are poorly defined and whose intrinsic structure does not differ significantly from the remainder of the corpus. It was also shown that during pregnancy the changes which occur in the isthmus are similar qualitatively and quantitatively to those of the remainder of the uterine musculature. Further, in the uterus through the fifth month of pregnancy it was not possible to distinguish the point of junction of the isthmic segment with the remainder of the corpus. In an earlier study of the Rhesus uterus during labor,³ the findings suggested that the portion corresponding to the lower uterine segment, instead of elongating during the first and second stages of labor as it is commonly believed to do, actually underwent longitudinal shortening. Since our present understanding of the lower uterine segment is incompatible with these observations, certain changes must be made in order that the concept may conform to the findings. It is the purpose of this paper to present a working hypothesis which includes the factual observations and deletes certain of the inferences which are not based directly upon fact.

The historical aspects of the literature dealing with the lower uterine segment, and also the key articles, have been summarized by Stander,⁴ and need not

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II. A Suggested Hypothesis

The Derivation and Boundaries of the Lower Uterine Segment.—

It has been shown elsewhere,² and recently confirmed,⁷ that the cervix is basically a fibrous structure. In considering the contractile function of the uterus, it is, therefore, necessary that this portion be distinguished from the muscularis; and it is considered proper that the inferior boundary of the lower uterine segment be located at the fibromuscular junction of cervix with corpus.

The delineation of the superior border of the lower uterine segment is less obvious. It may be stated unequivocally that a specific point of junction of upper and lower segments cannot be distinguished in the uterus up to the fifth month of pregnancy. One, therefore, infers that the lower uterine segment does not develop into a definitive, clearly evident structure until later. Since the



Fig. 1.—Lateral x-ray, metal clips on cervix. Early first stage of labor.

lower pole of the uterus (excluding the cervix) is roughly cup-shaped, it is apparent that there is a point along the uterine wall below which circumferential dilatation must occur in order for the baby to pass, and above which the diameter is already great enough that no such further dilatation need occur. It is considered that this point marks the junction of the lower and upper uterine segments, and that the level at which this point occurs in any given uterus is determined only by the relationship between the size of the presenting part and its level in the uterine cavity. In accordance with this thesis, one may define the lower uterine segment as the portion of the uterine musculature which must

length, at which greater length the fiber manifests the same tension as it did prior to contraction. Mceystasis is considered as occurring in the lower segment during the first stage of labor, since, according to present understanding, this segment undergoes both circumferential dilatation and longitudinal elongation, together with progressive thinning.

Before this theory may be modified, the inferences must be distinguished from the factual observations. The former may be deleted at will from any new hypothesis; the latter must necessarily be included and fully accounted for. The factual observations include the following:

A. Prior to the onset of labor the lower uterine segment is often thinner than the upper. The transition between the two is often abrupt, and, at this stage or in normal unobstructed labor, it is known as the "physiologic retraction ring."

B. The lower uterine segment becomes progressively thinner as labor advances.

C. The upper uterine segment becomes progressively thicker as labor advances.

D. In both normal and obstructed labor, the junction of the upper and lower uterine segments is increasingly distinct, and advances cephalad as labor continues.

E. In obstructed labor, uterine rupture occurs through the thinner lower uterine segment.

To these well-known observations, one may now add the following:

F. During the first half of pregnancy the point of junction of the upper and lower segments is not distinguishable. A physiologic retraction ring is not present until some time in the last half of pregnancy.

G. There is no intrinsic structural difference in the musculature of the upper and the lower poles of the uterus above the level of the cervix.

H. Study of the Rhesus uterus, which is similar in type to that of the human being, indicates that the lower pole of the uterus shortens progressively during the first and second stages of labor.

I. In normal labor, the lips of the cervix rise in the pelvis as dilatation proceeds. At full dilatation they reach the plane of the inlet, as is demonstrated by x-ray studies made with metal clips upon the anterior and posterior lips.⁶

The hypotheses which may be deleted, since they are not based upon observation are the following:

A. That the lower uterine segment takes its origin specifically from the isthmus uteri of Aschoff. Recent work has shown that the isthmic segment is subject to much variation and cannot be considered as a discrete and clearly defined anatomic entity. If these observations are accepted, then the isthmic segment should be viewed as an indefinite, variable portion of the lower pole of the corporeal musculature; and one may not correctly assume that the lower segment comes specifically and solely from the isthmus uteri of Aschoff.

B. That the lower uterine segment is a passive structure in labor. It has been shown that the musculature of the lower segment is anatomically similar to that of the upper segment, with two exceptions which are considered as not relevant to this discussion (these are an abundance of sensory nerve endings in the lower pole of the uterus, and also a greater amount of elastic tissue). Since the lower segment is a muscular structure, there is no reason to suppose that it would not contract to the best of its ability, just as does the upper segment. Also, the demonstration that this portion shortens in the Rhesus uterus during the first stage suggests that, indeed, it is quite as active as the upper portion of the uterus.

be overcome by the force of uterine contractions pulling against the now-taut uterine supports, these being the sites upon which the uterus gains its purchase. (Mengert⁹ has shown that of these supports the transverse cervical ligaments are the most important, the pubocervical fascia and the uterosacral ligaments less so.) Further changes in the uterus are considered as being wholly dependent upon the amount of effort which is expended by the uterus in overcoming the

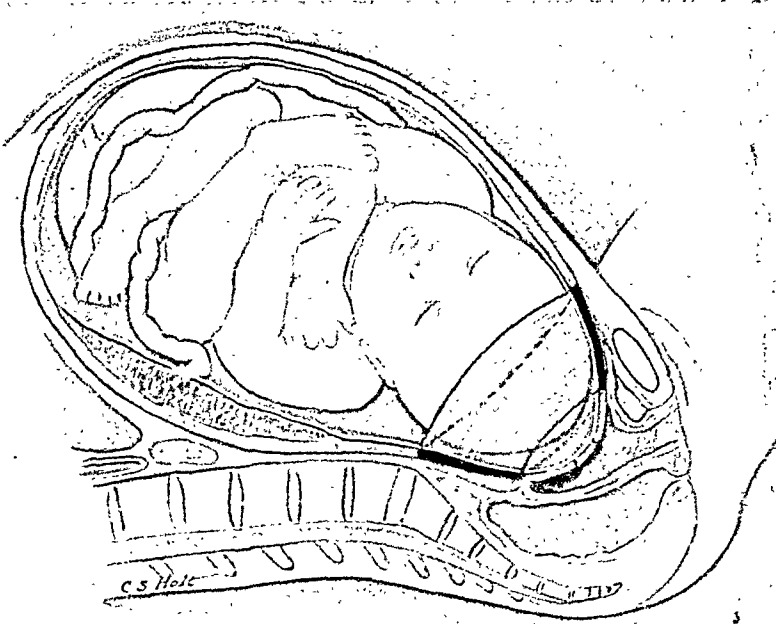


Fig. 3.

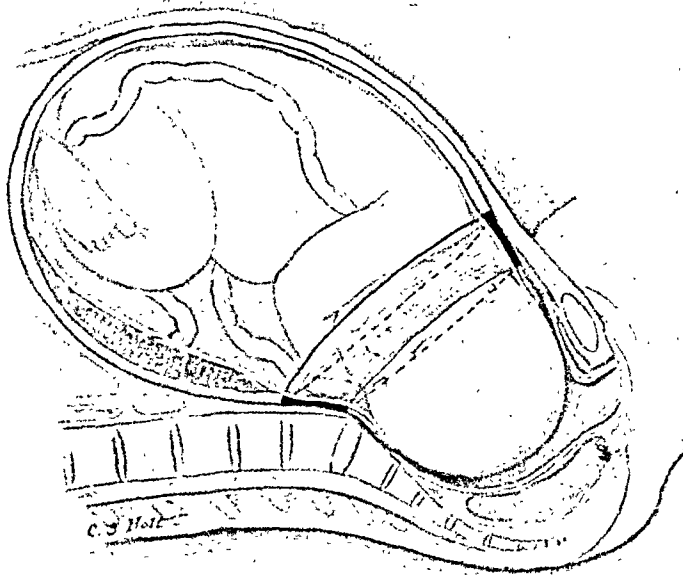


Fig. 4.

obstruction which is offered. If the obstruction is negligible, one would expect the uterus to shorten as a whole and empty itself. If there is significant obstruction to be overcome, however, such that advancement with each contraction is disproportionate to the attempt at progressive shortening which occurs in the

undergo circumferential dilatation. It is considered that this differentiation may begin either in early labor, or in the uterine adjustments which immediately precede labor (Fig. 3).

The Physiologic Behavior of the Lower Uterine Segment During Labor.—

The evidence which is available suggests that brachystasis occurs not only in the upper uterine segment, but rather that it is a fundamental property of pregnant uterine muscle, occurring throughout the entire musculature. As this occurs in the lower segment proportionately to that in the upper, this area is necessarily dilated as it pulls up about the presenting part. And thinning is a necessary accompaniment to this circumferential dilatation of the lower pole of the uterus. Longitudinal shortening of the lower uterine segment, with consequent dilatation and thinning, are considered to proceed gradually, progressively, from above downward, until ultimately the cervix itself is involved and



Fig. 2.—Same patient as Fig. 1. Late second stage.

full dilatation of the cervix is reached. Given a normal circumstance, at this stage one finds the upper uterine segment thickened by brachystasis, and also shortened in the same process; the lower uterine segment shortened by brachystasis but thinner because of circumferential dilatation; and the cervical lips at about the level of the inlet (Fig. 4). This stage is beautifully shown in Eastman's recent sagittal section,⁸ illustrated in Fig. 6.

If at this time there were no obstruction whatever to the passage of the baby, delivery could be accomplished by gravity merely by placing the patient in the erect posture. Even in entirely normal labors, however, some moderate obstruction is offered by the maternal soft parts and the bony pelvis. This must

uterine muscle, it is apparent that certain uterine adjustments must result. If the cervix could be pulled higher in the pelvis with successive pains, it is suggested that upper and lower segments would continue to shorten proportionately. However, since the cervix can go no higher, being held by the taut uterine supports, and since powerful brachystatic contractions continue, it is evident that the weakest portion of the uterine musculature must give way. The weakest portion, as mentioned above, is the portion which has been excessively thinned by circumferential dilatation. It is suggested that at this time only does elongation occur in the lower uterine segment (Fig. 5), that is, in the presence of significant uterine effort in the second stage of labor in the face of obstruction, either relative or absolute. It is suggested further that the early phases of this elongation may be through a me cystatic mechanism, as defined above. If the disproportion is not overcome and labor continues, uterine rupture must necessarily occur through the elongating lower uterine segment.

Summary

The present concept of the lower uterine segment is briefly reviewed. Revision of this concept is made necessary by certain recent work, the essential features of which are outlined.

To conform to these observations, it is suggested that the inferior border of the lower uterine segment be placed at the fibromuscular junction of cervix with corpus. It is considered that the superior border of the lower uterine segment occurs at the point along the uterine wall below which the uterus must dilate in order to allow the baby to pass. The lower uterine segment, therefore, is defined as the portion of the uterine musculature which must undergo circumferential dilatation during labor, its extent being dependent upon the size of the presenting part and its level in the uterine cavity. The available evidence suggests that brachystasis, with retraction, occurs in this segment just as it does in the upper, and that thinning in the first stage of labor is due not to passive elongation, but rather to active shortening of the cup-shaped lower pole with dilatation as it is pulled up about the presenting part.

It is believed that under normal circumstances, longitudinal elongation of the lower uterine segment occurs only during the second stage of labor when there is significant obstruction to be overcome.

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Discussion

DR. FREDERICK H. FALLS.—The work here presented must be considered as an attempt to explain the very interesting clinical phenomena which appear in the pregnant uterus, especially in the region of its lower pole during pregnancy and labor. As pointed out by Dr. Danforth, the last word has not been said previously and certainly not tonight. However, if we do not talk about, speculate on, and experimentally observe these clinical phenomena, we never will advance our knowledge concerning them.

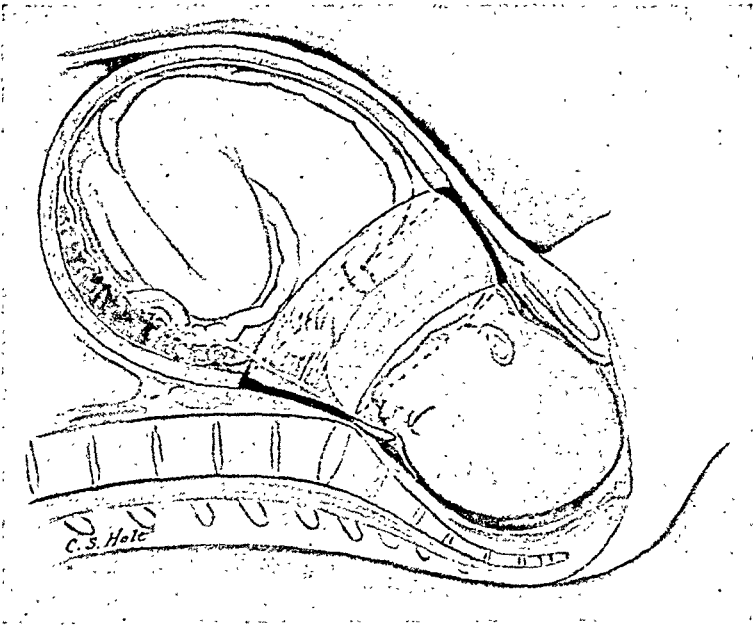


Fig. 5.

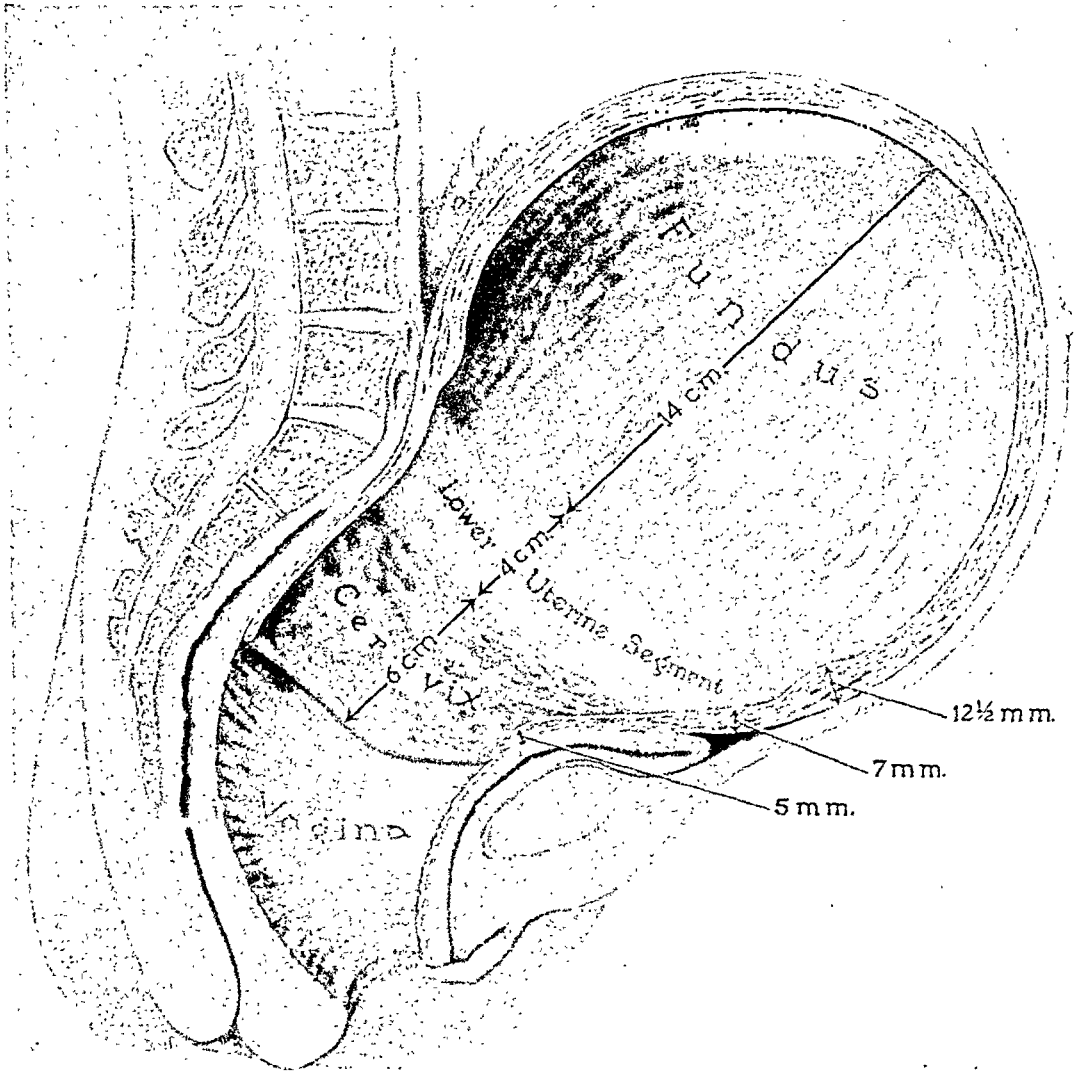


Fig. 6.—(From Obstetrical and Gynecological Survey. Williams and Wilkins Company, Baltimore. Courtesy of Dr. N. J. Eastman.)

has its origin in the last trimester of pregnancy and may be of sufficient length to admit the passage of a baby through it at cesarean section, long before the end of pregnancy. Does this signify that the separation of the uterine corpus into upper and lower segments is a growth process, the accompaniment of the developing pregnancy? Although the lower segment has some contractility, its motility in labor does not compare with the upper segment. Following the delivery of the baby at cesarean section, the walls of the lower segment remain flabby and thin whereas the upper segment promptly thickens. If the lower segment contracted actively in labor, would it not exhibit more muscular tone at this time? We have assumed that the low cesarean section was carried out in the lower uterine segment. Is it probable that the incision extends into the cervix and that it is not limited to the lower uterine segment? One other clinical observation that troubles me is the effacement of the cervix. As the internal os disappears and more and more of the cervical canal becomes obliterated, what effect do these changes have on the lower uterine segment? These are a few of the questions which this excellent presentation has raised in my mind. No doubt further work will fit our clinical experiences into these new basic concepts.

DR. A. C. IVY.—Some of the remarks made by the discussers reminded me of the reason I became interested in the subject of the physiology of the uterus. Dr. Rudolph came to me many years ago and told me about a case of obliquity of the uterus, which indicated to me that the uterine musculature manifested physiologic properties and a coordination of parts analogous to the heart and stomach, and that certain motor abnormalities must be due to a disturbance of the coordinating mechanism and contractility of the uterine musculature. For example, when Dr. Falls mentioned the elongation of the softened lower pole of the uterus which he has observed, to me that can only be explained by a physiologic loss of tone in the lower portion of the uterine musculature which we commonly refer to as the lower uterine segment. The contraction of one half of the body of the uterus more vigorously than the other half will cause obliquity.

When one stops to consider the question, how is it possible for labor to make any progress, for dilatation and effacement and descent to occur without brachystasis, we are forced to the conclusion that brachystasis of the longitudinal musculature is a *sine qua non* for these processes. It simply has to occur, and there is no other way to explain progress. Thickening of the shortened muscle has to take place.

As is true for all physiologic processes, we should not expect the process of labor to be stereotyped. We should not expect it to occur exactly the same way every time. In order to obtain an acceptable view of the normal variations of the behavior of the uterus in labor, we need more evidence from frozen sections such as submitted more recently by Dr. Eastman. We need more information of the type submitted by Dr. Danforth. It is with evidence of this sort that we shall resolve in the course of time the differences of opinion relative to the physiologic anatomy of the uterus in pregnancy and labor.

I believe the evidence that has been assembled by Dr. Danforth emphasizes the fact that, prior to the development of the physiologic retraction ring, no one can put his finger on the wall of the uterus and state that this is the junction of the upper and lower segments. The concept of the junction submitted by Dr. Danforth provides a new way of defining the junction. I suspect, when all the evidence is in, we shall find that the junction and the physiologic retraction ring are identical.

We need such evidence as follows to support the relationship of what we conceive to be the site of junction of the upper and lower segments and the anatomic internal os. When the occasion arises that the uterus has been exposed and the physiologic retraction ring has been seen and measured, some nonabsorbable, preferably opaque material should be inserted so as to label the retraction ring, preferably at three points, right, left, and anteriorly. Then, if, on making an x-ray or an anatomic examination, it is found that the nonabsorbable material is located at the level of the anatomic internal os, the question would be settled. It would be better, of course, if a case were at hand in which later a hysterectomy would be indicated so that the specimen could be examined anatomically. We have such evidence for the monkey and there is no good reason why the uterus of the monkey should differ significantly from the human uterus.

I think we will all agree with the writers that the lower uterine segment cannot be a passive structure as has been contended by some. Where else in nature are found muscle cells that do not contract? One cannot argue from this, however, that it is the contractions of the lower uterine segment fibers that are the principal factors in the dilatation of the cervix and its upward retraction. The downward push of the uterus on the presenting part would seem to be more logical explanation, causing a wedge like opening of the cervix and lower fibers of the lower uterine segment. There is a small but very important group of cases for this discussion, in which the fibers of the lower uterine segment are elongated to such an extent that the clinical appearance leads one to believe that the woman has a full bladder. The first time I saw this phenomenon in a woman in labor I was curious as to the behavior of this part of the uterus after the pains became strong. Fearing rupture, I stayed in continuous attendance on the case. Labor progressed in a perfectly normal manner and spontaneous delivery resulted. There was no tenderness of the lower uterine segment, in spite of the obvious elongation of its fibers and the height of the ring marking the junction of the lower and upper uterine segments, and no other clinical sign of threatened rupture of the uterus.

Another clinical fact that I should like to point out is the difference between the ring at the junction of the upper and lower uterine segment and the muscle either above or below during labor. The best way to appreciate this is to put one's hand into a uterus that is contracting in a case of dystocia. When the hand is in the lower uterine segment there is very little compression. When an attempt is made to pass the constriction ring, the muscle is found to be in continuous tetanic spasm and as hard as a steel band. Above this, the uterine muscle is contracting and relaxing rhythmically but futilely because of spasm of the ring. Here, then, is a continuous spasm of one part of the upper uterine segment and a contraction and relaxation of another part.

I am not convinced of the appearance of brachystasis during labor. If this were so, then there would be a continuous thickening of the whole upper uterine segment during labor. In doing a number of classical cesarean sections, I have not been impressed by the fact that the upper uterine segments of those in labor were thicker than those not in labor, even when the operation was done under local anesthesia, which would obviate the possibility of the anesthetic agent's causing secondary relaxation of the brachystasic contraction.

We have a specimen confirming Dr. Danforth's observation that the lower uterine segment does not form until the latter months of pregnancy. I removed a five months' pregnant uterus in a girl with active tuberculosis at the insistence of the medical department because of a rapidly progressive pulmonary tuberculosis. I hardened this specimen in formalin before opening and measured the thickness of the uterine wall. There was no contraction ring noted and very little difference between the upper and lower uterine segments.

DR. M. EDWARD DAVIS.—The derivation and the physiologic behavior of the lower uterine segment has been of more than academic interest for very many years. The changes incidental to the development of the uterus for parturition are of fundamental importance in order to understand the mechanism of labor and delivery. However, as the authors point out, there is considerable difference of opinion concerning these basic changes.

The uterus must differentiate into three distinct parts in order that delivery can be accomplished. The long, closed cervix must be slowly converted into a thin-walled passageway which connects the corpus and the vagina and plays a passive role during labor. The structure of the cervix lends itself to this role, for, as Danforth has pointed out in a previous communication, it consists of fibrous tissue without muscle cells.

The corpus of the uterus is differentiated into an upper and a lower segment. The upper segment with its thick muscular wall is the actively motile portion. It provides the activity necessary to alter the lower segment as well as to convert the cervix into a passive canal by the process of effacement and dilatation. The lower segment, largely muscular but containing much elastic tissue, has a fixed inferior border at the fibromuscular junction with the cervix and corpus. Its superior border, however, varies considerably, depending on many factors such as the length of the pregnancy, the parity of the patient, the length of labor, the degree of obstruction to be overcome, and the size of the baby. It must likewise provide sufficient room to allow the baby to pass through its lumen.

This concept presented by the authors is supported by much sound experimental data. However, many clinical observations must be reconciled with it. The lower uterine segment

VASCULAR PATTERNS IN THE HUMAN OVARY*†

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OVARIAN spiral arteries, long forgotten after their original description in the literature, have been rediscovered recently, and much concerning their nature and functions has been learned.¹ Instances may be cited from medical history illustrating a cycle of initial discovery of a fact, its passing into oblivion, and rediscovery at a later date. The latter may occur at a favorable time when newer data are available in allied branches of science sufficient to give the original observation an important meaning. One such example is that of the discovery of William Hunter in 1774² of the spiral arterioles in the human endometrium. In 1936, these were rediscovered by Daron³ in the monkey, *Macacus rhesus*. By this time, knowledge of the physiology of the uterus was sufficiently advanced so that certain functions could be ascribed to endometrial spiral arterioles. A rather similar situation exists with respect to the spiral arteries in the ovary.

Farre⁴ first made mention of spiral arteries in the human ovary in 1858. His description is most accurate but limited in scope, and the illustration in his article of their location and distribution in the ovary is inadequate. Belou⁵ in 1934 presented stereoscopic radiographs of spiral-like arteries in the human ovary, and referred to them as balls of helical vessels. In 1947, it was observed¹ in the ovary of the rabbit that the arterial branches in the hilus of the ovary are spirals of gradually diminishing diameter. These lie along the length of the hilus of the ovary. In further studies,⁶⁻⁸ it was shown that adaptive alterations occur in the spiral arteries when the ovary changes in size. When the size of the ovary was increased by injection of chorionic gonadotrophin into the rabbit, the helical spirals became extended, usually in an even, orderly fashion. In this way, they became adapted to the enlarged ovary. In addition to extension, lateral flattening of the coils also occurred. The effect is transient, since regression occurred following a decrease in ovarian size as stimulated follicles became atretic. Spiral configuration is restored largely by the sixth day following intravenous injection of the gonadotrophin, although flattening of the coil lasted as late as the ninth day. This is the effect of normal ovulation and luteinization. When corpus hemorrhagicum cysts occurred in the rabbit ovaries following injection of chorionic gonadotrophin, distortion of localized portions of the spiral artery was observed in the vicinity of these cysts. It was suggested that distortion of the spiral artery might contribute to cystic development through the mechanism of altered local hemodynamic relations in the ovary during the active growth phase of the follicle under stimulation of the gonadotrophins. This observation of an association between distortion and cysts suggested that spiral arteries in the ovary normally serve to regulate the local blood pressure within the ovary.

*Presented at a meeting of the Brooklyn Gynecological Society, April 2, 1948.

†Aided by grant from the Kate Lubin Research Foundation, Inc.

The upper and lower segments of the uterus are physiologic as well as anatomic parts of the uterus. The fact is, the lower segment is not passive, as Dr. Falls properly emphasized. It is contracted, or, in other words, resists stretch; and if it were not contracted it would not resist stretch and it would balloon out. Even though the lower segment is an active segment, it is relatively passive when compared to the upper segment. The musculature of both segments contracts and manifests changes in length and tension.

DR. LOUIS RUDOLPH.—It is rather unfortunate that the word "ring" was ever added to this junction. The second stage frozen section of Braune shows a definite ring. The second stage sections of Chiara show a tapering of the thickened upper segment into the thinned lower segment. The junction of the upper and the lower uterine segments is just a tapering of one segment into the other in the region of the fixed anterior uterine peritoneum. Some years ago I wrote to one hundred and four leading obstetricians, inquiring if they had seen or felt a ring during the performance of cesarean section. The answers were in the negative.

The brachystasis is manifested mainly in the fundus uteri of the upper uterine segment and then tapers downwards into the lower uterine segment. According to Aschoff the junction of the upper and the lower uterine segments, or the physiologic retraction ring, is in the region of the anatomic internal os. An intrauterine examination after the delivery of the placenta presents a firm thickened upper segment and a flaccid lower segment, the junction of which is abrupt, due to the 3 to 4 cm. thickening of the upper segment and a thinned lower segment which is about 1 cm. thick. This junction is not a ring, but, as Barbour described it, a ledge, ridge, or a rim between the two segments.

The next point I want to dwell upon is the cervix. Dr. Davis still has the idea that the cervix is opened or dilated purely by the mechanical factor of the upper uterine segment which pushes the presenting part through the cervix. If we study parturition in the dog, we have a beautiful example of what nature does. With the fingers in the cervix after a pup is born, the cervix remains relaxed until the next pup descends to dilate the cervix. The cervix is left relaxed for the oncoming pup.

Dr. Danforth has presented definite evidence of the fibrous nature of the cervix with muscular tissue in the main of 10 to 15 per cent, which I can substantiate. Recently we studied 40 postpartum patients to determine the return of normal topography of the cervix. Immediately after the delivery the cervix is thin, except the anterior lip which is about 4 to 5 cm. thick. On the third or fourth postpartum day, the postpartum cervix returns to its normal topography. Is this return due to fibrous tissue readjustment or do the small muscle elements play a role in its return to normal?

Does the fibrous tissue have a function? What is the physiology of the fibrous tissue? We know clinically that the "obstetric" internal os and the external os have a sphincteric function during a Braxton Hicks version and during the delivery of the fetal head in a breech labor. What is this physiology of the spasmodic condition of the "obstetric" internal os and the external os in view of the fact that the cervix is nearly wholly fibrous? The question is, how much muscle tissue is necessary in the fibrous cervix for sphincteric property?

When we think of brachytasis of the upper uterine segment, we must realize that the circular me cystasis or dilatation of the cervix is coordinated to anatomic changes of the upper uterine segment by brachystasis.

DR. DANFORTH (Closing).—May I emphasize again that the thesis which we have presented is an attempt to outline what would happen if labor were to proceed in an entirely "normal manner"? However, it is questionable whether any of us has ever seen such a labor, and if we did see one in the future, whether we should recognize it as such. In answer to Dr. Rudolph's question concerning the amount of muscle which is necessary for sphincteric function: in occasional cervixes which are examined histologically with contrast stains, small accumulations of muscle tissue are found which conceivably might be capable of functioning as a sphincter. In the majority of cervixes, however, muscle tissue is extremely sparse, amounting to perhaps 10 or 15 per cent of the total cervical tissue, and is diffusely scattered; it would seem extremely difficult to ascribe sphincteric possibilities to this muscle.

Fig. 3.—Injection-corrosion preparation of a cast of the ovarian arteries from a patient menstruating regularly at the time of operation. A 30-year-old woman, para ii, gravida iii, having a fibroid uterus. Blood pressure 110/80. Menstruating regularly. Surgical specimen. Hysterectomy and bilateral salpingo-oophorectomy. Uterine artery injected. Note especially the profuse arterial branching, extreme crowding of the arteries and the large, loosely woven body to the right which is the cast of the blood vessels of a corpus luteum (large arrow). The small structure to the left (small arrow) is a follicular cyst which was injected. Extended tertiary spiral arteries can be seen in the vicinity of the corpus luteum and cyst. Compare with Fig. 2 and Fig. 1. Stereoscopic view ($\times 1\frac{1}{2}$).



Fig. 1.—Vinylite cast of the main ovarian artery in human ovary that was grossly sclerotic. The patient was a 53-year-old woman, para ix, gravida x with a history of nephritis and diabetes mellitus for eight to ten years prior to death. Blood pressure 210/112. Menopause in 1943. Postmortem specimen. Ovarian artery injected. Note spiral configuration of cast of this main or primary ovarian artery at one point, whereas the remainder of the ovarian artery is irregular and undulant. The branches are sparse, thin, shortened, and widely spaced. Such branching appears to denote ovarian inactivity. Compare with Fig. 6. See Table I, A, no. 12. Stereoscopic view ($\times 2$).



Fig. 2.—Injection-corrosion preparation of ovarian arterial pattern from a patient with recent menopause and a proliferated endometrium. A 54-year-old woman, para i, gravida vii, with past history of breast carcinoma and tumor of uterus. Blood pressure of 138/80. Last menstrual period 1945. Surgical specimen. Hysterectomy with bilateral salpingo-oophorectomy (fibroid uterus). The ovaries were grossly sclerotic. Uterine arteries injected. Note the characteristics of branching with parallel appearance of branches as they proceeded to periphery of ovary. Compare with Fig. 3, where branching is more profuse, and with Fig. 1, where branches are sparse and small. The dense mass of plastic lying over the middle of the main ovarian artery and extending downward is an artifact caused by plastic that escaped from a ruptured vessel. See Table I, B, no. 23. Stereoscopic view ($\times 1\frac{1}{2}$).



the secondary arterial branches are the smallest arteries demonstrated. From these the small arterioles and eventually the capillaries arise. These tertiary vessels regularly show the greatest spiralling.

Spiralling in all branches, but particularly in the tertiary vessels, occurs in the form of a helix with a gradually diminishing diameter. It proceeds in a counter-clockwise direction as originally observed in the rabbit.¹ The tightness or compactness of the spiral is influenced by the presence or absence of pathology, by the presence of cysts, large Graafian follicles or corpora lutea, by the menopause, and apparently also by engorgement of the venous system of the ovary.

Evidence that an extension of the spirals and some flattening of the ovarian spiral arteries occurs in relation to the presence of localized structures within the ovary (follicles, corpora lutea, and cysts) has been observed, and will be described in a future publication.

In rabbits an orderly sequence of extension and regression of the spiral arteries was demonstrated following injection of gonadotrophins.^{6, 7} This, of course, could not be done in the human beings.



Fig. 4.—An injection-corrosion preparation of the veins in the ovary from a regularly menstruating subject. A 39-year-old woman, para ii, gravida ii, with past history of hypertension and kidney disease. Blood pressure 170/100. Postmortem specimen. Ovarian vein injected. Note especially the venous configuration, the pampiniform plexus, the tortuosity, irregularity, flattening, anastomosis and the absence of spiralling. Compare with arterial casts and with Fig. 5. Observe how difference in thickness and density of the plexus may affect crowding of arteries (x8).

Abnormal Adult Ovary.—Early in this work an arterial cast of a 53-year-old woman with diabetes, nephritis, and hypertension of many years' standing was obtained. The patient had not menstruated since 1943. It was remarkable to observe the unusual appearance of the arterial branches coming off the main ovarian artery. These were observed to be sparse, broadly-spaced, thin, and shortened. In fact, the vessels appeared to indicate marked inactivity, as compared to the luxuriant branching noted in ovaries of a younger group of patients in the reproductive period of life (Fig. 1). These branches were lying close to the main ovarian artery. There was only a slight amount of spiralling present (compare Figs. 1 and 3).

A similar configuration to the above was noted in three other specimens (see Fig. 6). The patients from whom these preparations were made had in common: (1) age; they were in the fifth decade of life or over; (2) hypertension; (3)

In the present work, the patterns and distribution of the ovarian spiral arteries in the human ovary were studied in order to ascertain the extent to which the conditions observed in the rabbit apply to the human. Following a modification of the technique originally employed, surgical and postmortem specimens of human ovaries were injected with vinylite plastic (vinyl acetate), and the vascular tree was subsequently isolated following the use of a corrosion bath.⁹

Technique

An 18-gauge hypodermic needle with blunted tip was inserted into the vessel to be injected. In some cases injection was made through the ovarian artery, and in others the uterine arteries were used. Equally good casts were obtained either way because of the free inosculation to which Farre refers, which exists between the uterine and ovarian arteries.⁴ The other arterial stump, uterine or ovarian, as the case might be, was clamped. In infant and fetal specimens, injection was made by way of the lower aorta. The tissues around the vessel were tied securely with a ligature.

A small amount of acetone was injected in order to prevent a premature hardening of the plastic. Colored vinylite solution was then injected as rapidly as possible. A time interval of fifteen minutes was permitted to elapse so that adequate hardening could take place. Following this the injected ovary was trimmed away from the surrounding tissue and placed in a corrosion bath, which consisted of 500 c.c. of water, 5 c.c. of hydrochloric acid, and one-fourth to one-half teaspoonful of pepsin. This bath was incubated at 37° C. The vascular casts were digested free of tissue in ten to fifteen days. In preparations from the fetus, however, only twenty-four hours were required for complete digestion to take place. Small adherent bits of tissue were readily washed away from the cast under a gentle stream of tap water or by careful rotation in a beaker of water. Thus far, sixty sets of ovaries have been prepared and carefully studied.

Results

Normal Adult Ovary.—The main ovarian artery as it courses in the hilus of the ovary is noted to be undulant, tortuous, with a degree of flattening. In only one case was there a regularly formed spiral for a short distance (Fig. 1). The branches of the main ovarian artery proceed from the hilus into the ovary in a parallel manner reminiscent of the teeth of a rake (Fig. 2). In an actively functioning ovary, or one containing many structures, such as cysts or corpora lutea, this configuration may seem obscure, but close examination reveals its presence. The basic pattern is best seen in inactive ovaries or in those less active or those beginning to undergo involution. In such cases the branching is not so profuse and hence does not confuse the appearance of the basic arterial pattern (compare Figs. 2 and 3).

Primary, secondary, and tertiary branches are noted arising from the main artery in the hilus. The primary trunks are usually tortuous or undulant with an occasional spiral. They are also usually flattened. The degree of crowding together among the various branches is dependent upon the presence and size of specialized structures in the ovary, such as cysts and corpora lutea. The space is also affected by the altered activity of the ovary, as in the menopause, and probably also by the size of the underlying veins in the pampiniform plexus (Figs. 1, 3, 4, and 5). Arising from the primary trunks are the secondary branches. These are smaller in diameter and show essentially the same characteristics as found in the primary branches. However, a greater tendency to spiralling is noted in the smaller vessels. The tertiary branches arising from

specimen. Hysterectomy and bilateral salpingo-oophorectomy. Uterine artery injected. See Table I, C, no. 30. Observe the profuse arterial branching. In the upper right portion of the cast indicated by the arrow, there is a cast of a locally injected corpus luteum. The right half of this cast shows venous drainage of the corpus luteum. Compare with Figs. 1 and 6. Note also the difference in the distribution of the veins and arteries. Stereoscopic view ($\times 1\frac{1}{2}$).



Fig. 8.—Injection-corrosion preparation of the arteries from a 42-year-old multiparous woman with cirrhosis of liver having menometrorrhagia. Blood pressure 120/80. Postmortem specimen. See Table I, D, no. 18. This patient had grossly sclerotic ovaries, yet showed numerous arterial branches. Grossly sclerotic ovaries do not, therefore, necessarily mean inactive ovaries. Compare with Figs. 1 and 6. These latter also had sclerotic ovaries. Stereoscopic view ($\times 2$).



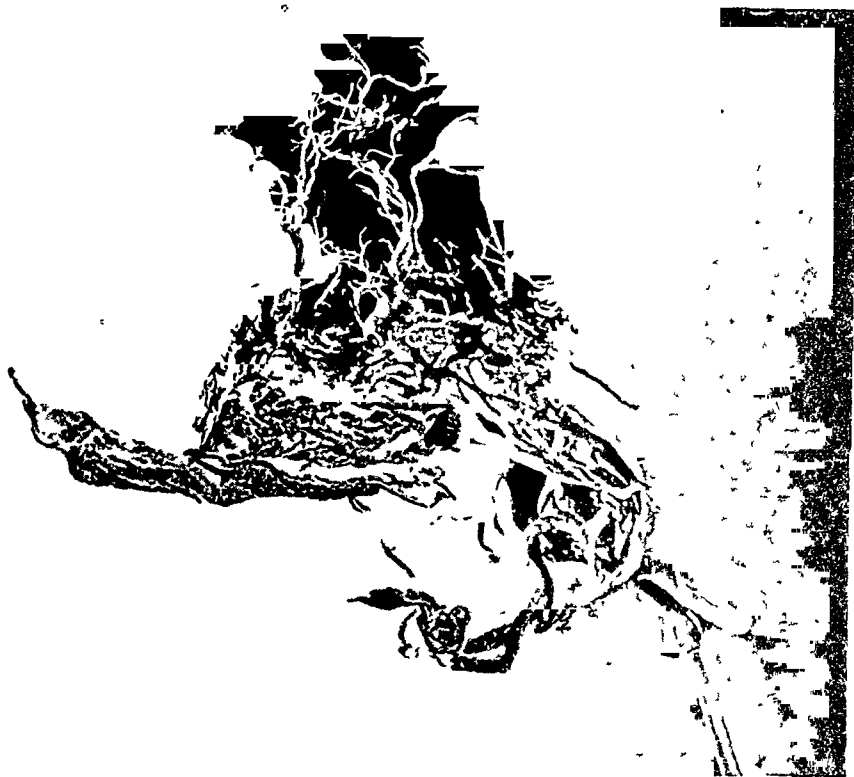


Fig. 5.—Injection-corrosion preparation of the venous network from a patient with a history of menometrorrhagia and fibroid uterus. Subject was a 34-year-old multiparous woman. Blood pressure 130/80. Total hysterectomy and bilateral salpingo-oophorectomy. Uterine vein injected. Compare with Fig. 4 ($\times 2$).



Fig. 6.—Injection-corrosion preparation of the arterial pattern in a 47-year-old multiparous woman six years past the menopause with history of chronic alcoholism and carcinoma of intestine. Blood pressure 160/90. Postmortem specimen. Uterine arteries injected. Compare with Fig. 1, since both are casts from postmenopausal women, and both suggest vascular inactivity. Arterial branches are sparse, thin, widely separated, small, and very slightly spiralled. See Table I, A, no. 28 ($\times 2$).

Ovaries were obtained from two other patients with hypertension (Table I, C, nos. 16 and 30) but not past the menopause. Their ovaries were not grossly sclerotic. These patients were below the fifth decade in age. The arterial casts from these ovaries reveal a relatively luxuriant and profuse appearance of the arterial branches (see Fig. 7).

Three patients are presented who were nonhypertensive and nonmenopausal (Table I, D, nos. 18, 39, 40, 41). Their ovaries were grossly sclerotic. These, too, showed an active or more profuse growth of arterial branches (see Fig. 8).

Although these data are few, they suggest that sparse, small, thin, and widely spaced arterial branching of the primary, secondary, and tertiary ovarian arteries (Figs. 1 and 6) are related to the menopause. This conclusion suggests that to the known trophic activities of estrogens we may now add also that of growth and development of the primary, secondary, and tertiary branches of the ovarian artery. Case number 23 in Table I, B and Fig. 2 suggests an ovarian vascular system that has not reached the end point of vascular involution represented by Figs. 1 and 6. The degree of involution is not complete. It may be that this patient had some extraovarian source of estrogenic stimulation. In fact, hyperplasia of the endometrium has been found in patients with long-standing menopause long after proved cessation of ovarian activity. It has been suggested that the adrenal cortex may have an estrogenic function after the ovary ceases its activity.¹³ The gross appearance of small sclerotic ovaries does not necessarily, therefore, portray quiescent vascular structures within the ovary.

Fetal and Neonatal Ovary.—The arterial cast from the ovary of a seven-month premature infant is shown in Fig. 9. In this, a slight degree of spiralling can be observed. In addition, preparations have been made from five other full-term and infant ovaries. The data are most interesting when tabulated in a chronological fashion, as in Table II.

TABLE II. CONFIGURATIONS OF OVARIAN ARTERIES IN PREMATURE AND INFANT OVARIES

NO.	AGE	GROSS OVARIES	ARTERIAL CONFIGURATION
31	Premature—7 month	Normal	Slight spiralling
44	Full term—stillborn	Normal	Slight spiralling
36	Full term—7 hr.	Normal	Slight spiralling
47	Full term—9 days	Normal	Excellent spiralling and more profuse branching
43	Full term—3 mo.	Two small atretic follicular cysts—left ovary	No spiralling
59	Full term—4½ mo.	Polycystic	Some spiralling with evidence of “paying-out” and many straightened arterial branches

From the seventh month of gestation until a short time after birth, growth and development of this vascular pattern in all specimens may be noted. This ranges from a slight degree of spiralling to excellent spiralling of the primary, secondary, and tertiary ovarian arteries. At three months of age, however, there is no trace of spiralling. At four and one-half months, some extended spirals may be seen and there are many straightened arteries in all branches.

The presence of cysts in infant ovaries and their relationship to arterial spiralling will be presented more fully in a future publication. It would seem, however, that the presence of spiralling, and its regression in fetal and infant ovaries, is dependent on a maternal hormonal influence. Maternal hormones have been recognized in the past as being an influential factor in newborn breast enlargement, lactation, endometrial bleeding and vaginal hypertrophy. In the latter case, desquamation begins in forty-eight to sixty hours post partum and

menopause; and (4) gross appearance of sclerotic ovaries. By grossly sclerotic ovaries is meant a condition in which the ovaries are small, white, hard, and rugose. They have a gross appearance which is indicative of inactive, or senile organs. Table I, A, nos. 12, 28, 32, 37, demonstrate in a comparative form all pertinent history with respect to these cases.

Fig. 9.—Injection-corrosion preparation of the ovarian artery from a seven-month premature infant that died shortly after birth. Injection by way of the lower aorta. Cast shows some slight spiralling of the tertiary arteries. Arrow points to ovarian area. See Table II. Stereoscopic view (x5).



TABLE I. PERTINENT CLINICAL DATA RELATIVE TO PATIENTS FROM WHOM ARTERIAL PATTERNS WERE OBTAINED

NO.	AGE	BLOOD PRESSURE	L.M.P.	GROSS OVARIES	ENDOMETRIUM
A. Subjects hypertensive and postmenopausal					
12	53	210/112	1943	Sclerotic	
28	47	160/ 90	1941	Sclerotic	
32	73	212/ 55	Many years	Sclerotic	Atrophic
37	51	160/ 96	1940	Sclerotic	
B. Subject nonhypertensive; recent menopause					
23	54	136/ 60	1945	Sclerotic	Proliferative
C. Subjects hypertensive and premenopausal					
16	42	170/100	Sept. 1947	Cystic	
30	43	170/100	Menometrorrhagia	Cystic	Early secretory
D. Subjects nonhypertensive and premenopausal					
18	42	120/ 80	Menometrorrhagia	Sclerotic	
39, 40*	46	140/ 80	Sept. 23, 1947	Sclerotic	Proliferative
41	47	150/ 65	Oct. 20, 1947	Sclerotic	Early secretory

*Nos. 39 and 40 were specimens from same patient.

Ovaries from another patient (no. 23, Table I, B) with a similar type of history and clinical findings as the foregoing ones were also studied. This patient differed, however, in that she was nonhypertensive, and her menopause was more recent. The endometrium still showed proliferative changes. The cast of her ovarian arteries, shown in Fig. 2, shows branches that are definitely smaller, thinner, and more widely spaced than those seen in more active ovaries (Figs. 7 and 8).

Observation of the venous vascular tree shows completely different characteristics when compared to the arteries.

Acknowledgment is hereby made to Dr. Silik H. Polayes for his kind assistance in making specimens and facilities available for this study. We are also indebted to Mr. Chester F. Reather, photographer in the Department of Embryology, Carnegie Institution of Washington, for his excellent photographs of the injection-corrosion casts of the ovarian blood vessels.

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Discussion

DR. S. R. M. REYNOLDS.—The essential features of Dr. Delson's work are twofold. He has, first, analyzed the normal vascular patterns of the human ovary and shown the homology of parts between these and the simpler structures found in the rabbit ovary. Second, he has shown that the coils of the ovarian spiral arteries depend upon estrogens for their growth, development and maintenance. This is clearly a factor of some consequence to the gynecologist who must understand how to deal with the problem of primary amenorrhea, if there are no other signs of hypopituitarism. I think that Dr. Delson did not emphasize the point sufficiently that the evidence is clear that in those instances in which no estrogen has been produced, long after the menopause, there are few or no spiral vessels. The condition is not related to either hypopituitarism or sclerosis. This is highly significant, and it may well have an important meaning in the cases of amenorrheic females 18 or 19 years of age with no evidence of anterior pituitary gonadotrophic secretion. It may mean that estrogen is needed as a stimulus for the blood vessels of the ovary. And if this premise is correct, maturity is in part the result of the gonadotrophic hormone acting through the ovarian cortex, stimulating growth, and building up an adequate ovarian vasculature over the years until there is full maturity of the ovary.

It is of interest to the morphologist that estrogens have this particular trophic action upon the coiled vessels of the ovary. They have an exactly similar action upon the coiled arterioles of the uterus. Okkels and Engle observed ten years ago that with complete estrogen deprivation only part of the uterine spiral arterioles degenerate, namely, the spiral arterioles of the endometrium. What there is in common, histologically speaking, between these vessels of the ovary and the uterus remains to be established.

Dr. Delson stated that one of the functions served by the ovarian spiral vessels is the lowering of the blood pressure within the ovary. That is a very handy method of controlling the local circulation because the ovaries are more or less closely attached to the uterus in its outer part, and when the uterus is pregnant the ovaries become displaced with the uterus. Isn't it a convenient mechanism that moves the regulator of local blood pressure with the

complete, infantile atrophy appears at the end of the first three weeks of post-natal life. Seventy-five per cent of infants will lactate until three to four months of age.¹⁰

Scammon,¹¹ investigating the subject of uterine growth, observed that the fetal uterus grows uniformly until the seventh month of intrauterine life. After this period, an acceleration in the rate of uterine growth occurs. He suggested that "growth of the uterus in the latter fetal months consists of a substrate of typical fetal growth plus a secondary growth increment, which presumably is due to an extra stimulus furnished by a hormone of placental or possibly ovarian origin. After birth, the organ loses this secondary increment but retains that resulting from the early fetal growth rate." Within a few days after birth, the uterus diminishes in size. However, a fortnight after birth the uterus is the size of that noted in 11-year-old females.¹²

From the evidence presented in Table II, and keeping the above discussion in mind, it is suggested that maternal hormones may stimulate the development of spiralling and branching of the primary, secondary and tertiary arteries in the ovary beginning late in fetal life. The action is most marked about one week after birth. Regression takes place over a period of several months after the maternal influence is withdrawn by parturition.

Ovarian Veins.—The casts of ovarian veins are quite different morphologically from those obtained from the arterial system and can be easily identified. We have confirmed Farre that the veins of the ovary drain into a pampiniform plexis⁴ in the hilar area. They are large, irregularly tortuous, markedly flattened, and often appear matted (compare Figs. 4, 5). The various branches anastomose with each other very frequently. This contrasts with the ovarian arteries which show no evidence of vascular anastomoses. Within the substance of the ovary, the veins end in small, straight channels that are never spiralled. Occasionally small, pouch-like protuberances were noted in larger branches in the vicinity of the hilus. Sometimes a beading may be noted in the medium veins that may be mistaken for spiralling on superficial examination.

Summary

A study of vascular patterns in the human ovary has been presented.

The vascular system in the human ovary is more complex than that of the rabbit. However, it shows helical spiralling with gradual diminishing diameters in the branches of the main ovarian artery. The function of spiralling in the ovarian branches of the arterial system are (1) adaptation of the vasculature to ovarian growth, and (2) to provide a mechanism for the reduction and regulation within the ovary of blood pressure.

A relationship exists between arterial spiral distortion resulting from ovarian cysts, corpora lutea, and the arrangement of the ovarian veins.

Characteristics of the ovarian artery and its branches have been described.

The relation of the condition of the vessels to ovarian activity and inactivity have been discussed.

It is suggested that there is a relation between growth and development of ovarian arterial branches and estrogenic activity in the adult.

Evidence is presented to show that branching of the arteries in the ovary from late fetal life to shortly after birth is under the influence of maternal hormones.

A SURVEY OF FUNCTIONAL UTERINE BLEEDING WITH SPECIAL REFERENCE TO PROGESTERONE THERAPY

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FUNCTIONAL uterine bleeding is a major problem in gynecology, as it frequently occurs in young individuals and causes such severe symptoms that treatment is imperative. Yet, by definition, the uterus is normal. Under these conditions, radical therapy such as hysterectomy or irradiation for the control of bleeding is to be avoided if possible.

It has long been recognized that the endometrial pattern of functional uterine bleeding is not uniform. Consequently, the response to therapy might also vary, depending upon the associated endometrial pattern.

With this in mind, an effort has been made to analyze cases of functional uterine bleeding seen in the gynecologic out-patient department at the Johns Hopkins Hospital, to determine the relationship between the endometrial pattern and the response to therapy.

Method of Case-Handling

Patients having functional uterine bleeding were subjected to an initial curettage. This procedure served the dual purpose of establishing the diagnosis and instituting the simplest form of therapy. There has been a satisfactory response in approximately 42 per cent of all cases treated in this clinic by a single curettage.¹ Only if abnormal bleeding recurred, was a case referred to the functional bleeding clinic for special consideration.

In 1942, the authors reported the results of progesterone therapy in cases of functional uterine bleeding associated with endometrial hyperplasia.¹ The present study extends to all types of endometrial patterns, but the method of therapy has remained essentially unchanged. An initial dose of 30 mg. of pregnenolone* a day was given orally for seven days. Therapy usually followed a suction curettage, as all patients were bleeding abnormally when treatment was begun. The Novak suction curette is preferred because, although it requires a slightly more complicated apparatus, it is more versatile in its use. With the continuous type of suction, rather than a plunger type, a discrete biopsy can be obtained or a fairly thorough curettement performed if desired. The initiation of therapy could not be related to any specific time of the cycle as the patients were not having cyclic bleeding. Twenty-eight days after the first progesterone therapy, the second course of seven days of medication was begun, using the same dosage. The third therapeutic cycle was given for from five to seven days beginning twenty-one days after the onset of bleeding following the second course of progesterone therapy. If, during the second and third months of therapy, the therapeutic response was satisfactory, that is, if the bleeding began within five days of cessation of therapy and lasted no longer than seven days, medication was discontinued. The patients were carefully watched during the next few months, and if excessive or prolonged bleeding recurred, therapy was resumed.

*Progesterone (Roche-Organon, Inc., Nutley, N. J.)

ovary as it moves? In the rabbit, I have measured blood pressure in the ovarian artery about a centimeter or two away from the ovary. The necessity for lowering of the blood pressure within the ovary is shown by the fact that the blood pressure in the ovarian artery is about 30 to 50 per cent that in the carotid artery. The necessity exists, therefore, for lowering rapidly the blood pressure in the ovary to near the level of the effective osmotic blood pressure in the plasma.

The effect of ovarian growth following gonadotrophic stimulation of the rabbit ovary shows that there is normally an even extension of the coiled artery. The effect is maximal at seventy-two hours after the injection of gonadotrophins, and over the next six days (as many stimulated Graafian follicles become atretic) the coil recovers.

In the rabbit the pattern is simple. However, Dr. Delson has seen that the same thing is occurring in the human ovary many times over since there are many more vessels. If we did not have the rabbit ovary as a basis of primary information, I doubt that we could understand the situation in the human, since the vasculature is so complex.

If cysts result from the injection of gonadotrophins, there is extreme distortion of the spiral arteries. The cysts are in the vicinity or, just distal to, the area of distortion.

The physiologic story that has been elaborated is opening up a new field of understanding of the relationship between the arteries and the flow of blood. In other words, if the latter is abnormal when follicles are growing rapidly cysts develop; if it is not abnormal they do not. There is reason to believe that hormonal stimulation produces generalized follicular growth; this normally gives rise to even extension of the spiral arteries. If the amount of follicular growth is excessive in some region of the ovary, then distortion of the spiral artery results, and with disorientation of the local hemodynamic relations, extreme swelling of the growing follicle ensues. I believe that this work of Dr. Delson's may open up a new chapter for the pathologist who is interested in interpreting the various kinds of ovarian pathology that he sees in the ovaries.

Dr. Delson's work shows, I believe, that these simple lesions which are so easily seen in the rabbit occur in the human being as well. However, instead of a single coiled vessel, there are numerous coiled vessels, and these offer multiple chances for localized ovarian dysfunction. The gynecologic pathologists will, I believe, tell us much concerning this unwritten chapter of gynecology.

with those reported by Jones in 1938,² but the out-patient department statistics vary somewhat. This variation probably reflects the fact that the criteria for the diagnosis of chronic endometritis during the year 1940 were apparently more liberal than in other years.

In both the out-patient department and the special clinic, endometrial hyperplasia comprised the largest group of cases on the basis of the original curettage, this being 69 cases, or 66 per cent of the special clinic group. To substantiate further the feeling that severe functional bleeding is most commonly associated with the pattern of endometrial hyperplasia, it is noted that, during the years 1940 and 1945, 54 per cent of the patients with endometrial hyperplasia seen in the general dispensary were referred to the special clinic, while only 10 per cent of those showing interval non-secretory endometrium and no appreciable percentage of the other endometrial types was referred.

The majority of patients in the special clinic group had been curetted for recurrences on numerous occasions. The results of study of the total 234 curettages performed on the 104 patients have been tabulated in Table III. In approximately 37 per cent of cases, the histologic picture changed in successive curettings from the same patient. The main variation, however, was between hyperplasia and interval nonsecretory endometrium (Table IV). It is significant that, in the present series at least, hyperplastic or nonsecretory endometrium never varied with a secretory pattern while the patients were having symptoms. Curettings taken to evaluate therapy when patients were asymptomatic have not been included. Many were secretory immediately after progesterogen therapy (Fig. 1). Only two curettements were made on patients who were having regular menses from six to eight months after therapy. Both showed secretory endometrium (Fig. 2).

The variations of pattern found in the secretory group corresponded to the menstrual dates except in the one instance of chronic endometritis. This curettage was done on a patient with thrombocytopenic purpura who had been bleeding profusely nine days.

Results of Therapy According to Endometrial Patterns

Endometrial Hyperplasia.—Sixty-nine of the 104 special clinic patients showed endometrial hyperplasia at the initial curettage. Forty-four, or 64 per cent, showed an unchanging hyperplastic pattern on every subsequent curettage, while 25, or 36 per cent, showed some variation (Table III). By far the most common histologic variation was between hyperplastic and interval nonsecretory endometrium. Several patients showed three different types of endometrial patterns on successive curettements during the seven-year period (Table IV).

TABLE III. CHANGE IN ENDOMETRIAL PATTERNS FOUND IN A STUDY OF 234 REPEATED CURETTAGES ON 104 SPECIAL CLINIC PATIENTS

ENDOMETRIAL PATTERN	NO. OF CASES FOUND AT ORIGINAL CURETTAGE	NO. OF CASES SHOWING NO CHANGE IN PATTERN	NO. OF CASES SHOWING CHANGE IN PATTERN
Hyperplasia	69	44 (64%)	25 (36%)
Interval nonsecretory	17	12	5
Endometritis chronic	3	1	2
Postmenstrual	0	—	—
Atrophic	2	2	0
Menstruating	0	1	—
Secretory	13	6	7
Total	104	65 (63%)	39 (37%)

While the bleeding symptoms were being controlled by hormonal therapy, attempts were made to evaluate the etiological factors underlying the condition. Routine laboratory studies consisted of a basal metabolic rate, blood cholesterol, fasting blood sugar, and a complete histologic blood study. Medical consultations were routinely requested, as were psychiatric consultations when indicated. Additional laboratory data, consisting of glucose tolerance tests, urinary 17-ketosteroid determinations, x-rays of the sella turcica and chest, as well as examinations of the visual fields were obtained only when indicated. Following the first two months of cyclic progesterone, some form of adjunctive therapy, consisting of diet or thyroid, was begun as indicated.

Material

A total of 104 cases were studied in the functional bleeding clinic during the past seven years. The records of 212 patients with functional bleeding seen in the gynecologic out-patient department during the years 1940 and 1945 were reviewed for comparisons. It is significant that only 36 cases, or 17 per cent of the above 212 cases, were considered suitable for study in the special functional bleeding clinic (Table I). This means that such patients had repeated attacks of prolonged or profuse bleeding not checked by curettage and were in the younger age group. That age has played a major role in determining which cases should be referred for consideration of conservative therapy is shown in Table II.

TABLE I. ENDOMETRIAL FINDINGS IN CASES OF FUNCTIONAL UTERINE BLEEDING

ENDOMETRIAL PATTERN	STATISTICS FOR OUT-PATIENT DEPARTMENT			STATISTICS FOR SPECIAL FUNCTIONAL BLEEDING CLINIC, YEARS 1940-1947	
	1940	1945	TOTAL PER CENT	PER CENT	ORIGINAL DIAGNOSIS
Hyperplasia	30 (16)*	25 (14)	26	66	69
Interval nonsecre- tory	26 (1)	21 (4)	22	16	17
Endometritis chronic	34 (1)	13	22		3
Postmenstrual	5	5			0
Atrophic	1	—			2
Menstruating	1	4			—
Secretory	24	23	22	12 (4)†	13 (4)†
Total	212 (36)			104	

*Indicates the total number of cases referred to the Special Functional Bleeding Clinic.

†Indicates the total number of true functional cases. See Table VII.

TABLE II. AGE DISTRIBUTION OF CASES SHOWING FUNCTIONAL BLEEDING WITH
NONSECRETORY ENDOMETRIUM

AGE IN YEARS	OUT-PATIENT DEPARTMENT CASES YEARS 1940 AND 1945		SPECIAL CLINIC CASES 1940-47	
	CASES	PER CENT	CASES	PER CENT
11 to 20	13	12	25	27
21 to 30	37	35	46	51
31 to 40	30	29	11	12
Over 40	25	24	9	10
Total	105	100	91	100

Endometrial Patterns

The types of endometrial patterns found in the groups of patients studied can be seen in Table I. The statistics from the special clinic agree quite well

TABLE IV. VARIATIONS IN PATTERNS WHICH OCCURRED WITH RECURRENCE OF SYMPTOMS AS SHOWN IN 130 SUBSEQUENT CURETTINGS FROM 104 CASES OF FUNCTIONAL BLEEDING

ENDOMETRIAL PATTERN AT ORIGINAL CURETTAGE	NO. OF SUBSEQUENT CURETTAGES SHOWING THE FOLLOWING PATTERNS					
	HYPER- PLASIA	INTERVAL NONSECRE- TORY	ENDO- METRITIS CHRONIC	POSTMEN- STRUAL	MEN- STRUAL	SECRE- TORY
Hyperplasia (69)	71	27	4	0	0	0
Interval nonsecretory (17)	10	9	3	1	0	0
Endometritis chronic (3)	1	1	0	0	0	0
Atrophic (2)	0	0	0	0	0	0
Secretory (13)	0	5	1*	1	1	0

*Obtained after a profuse nine-day menstrual period in a patient with thrombocytopenic purpura.

Fifty-six of the sixty-nine cases were considered suitable for progesterogen therapy and in this group there were no therapeutic failures (Table V). The establishment of regular menses while on therapy was the criteria of success. Two patients had subsequent x-ray castration because of recurrences. These women were both parous and in the older age group, one being 42 years old at the time of x-ray therapy. One patient had a bilateral salpingectomy and hysterectomy subsequently because of pelvic inflammatory disease.

TABLE V. RESPONSE TO PROGESTERGEN THERAPY IN 74 CASES OF FUNCTIONAL UTERINE BLEEDING SHOWING NONSECRETORY ENDOMETRIUM

ENDOMETRIAL PATTERN	CASES TREATED	SATIS- FACTORY RESPONSE	UNSATIS- FACTORY RESPONSE	RECUR- RENCE OF SYMPTOMS	NO RECUR- RENCE
Hyperplasia	56	56	0*	31 (55%)	25 (45%)
Interval nonsecre- tory	15	13	2†	7	6
Endometritis chronic	1	1	0	1	—
Atrophic	2	2	0‡	1	?
Total nonsecre- tory treated	74	72	2	40	31

*Two subsequent x-ray castrations in older parous women with recurrences. One subsequent hysterectomy, bilateral salpingectomy because of inflammatory disease.

†One patient had an ovarian neoplasm and the other a concomitant pelvic inflammatory disease which was controlled by chemotherapy.

‡One patient treated for recurrence elsewhere by intrauterine radium.

There were five atypical responses. Cases were considered atypical in response to therapy if the patient did not stop bleeding within eight days after cessation of the first progesterogen therapy; if bleeding recurred before 28 days after beginning of the first progesterogen course; or if bleeding lasted over six days following any subsequent course of progesterogen.

Of the fifty-six successfully treated cases, 25, or 45 per cent, had no recurrence of symptoms after the first three-month course of progesterogen therapy. If these 25 cases are analyzed as to adjunctive therapy, we find that 13, or about 50 per cent, had no other therapy. This might suggest that progesterone itself effects a cure. Thyroid medication was indicated and used, apparently successfully, in six patients with basal metabolic rates below -5 per cent or blood cholesterol values above 250 mg. per cent; an additional two patients were treated with desiccated thyroid and high protein, low caloric diets; three patients were treated by diet alone.



Fig. 1, A.—Curetings obtained immediately before therapy. Photomicrograph. Low power.



Fig. 1, B.—Curetings from the same patient after a total of 402 mg. of pregnenolone over a period of seven days. This dosage is necessary to produce a secretory pattern but half the amount will control the bleeding symptoms. Photomicrograph. Low power.

Thirteen cases were not treated with progesterone. Of these, five were treated successfully by high protein, low calorie diets with supplementary vitamins; two responded to thyroid, 0.1 Gm. (1½ grains) a day; two, with bleeding associated with pelvic inflammatory disease, were treated with douches and chemotherapy. Three patients in the menopausal group and an additional one with hypertension were advised to have irradiation therapy.

Forty-eight of the fifty-six women were married and ten of them subsequently became pregnant (Table VI).

TABLE VI. OBSTETRICAL HISTORIES BEFORE AND AFTER PROGESTERONE THERAPY OF PATIENTS WITH NONSECRETORY ENDOMETRIUM

ENDOMETRIAL PATTERN	CASES TREATED	MARRIED	PREGNANCIES BEFORE TREATMENT	PREGNANCIES AFTER TREATMENT
Hyperplasia	56	48	32	10
Interval nonsecretory	15	12	5	1
Endometritis chronic	1	0	0	0
Atrophic	2	1	0	0
Total	74	61	37 60%*	11 18%*

*Of married women.

The following case report is presented in detail because it seems to represent perhaps the most serious problem in a consideration of functional uterine bleeding: *the differentiation of benign endometrial hyperplasia and adenoma malignum*. It may serve as a warning that patients with very small malignancies of the fundus may respond to cyclic progesterogen therapy if the major portion of the bleeding is due to an associated endometrial hyperplasia. It is, therefore, extremely necessary to have thorough curettages in all cases before therapy is begun. In addition, endometrial biopsies should be obtained before patients with recurrent symptoms are treated, if a period of a year or more has elapsed since the original curettage.

Mrs. E. G., a 54-year-old white woman, para 3-0-0-3, had been bleeding profusely and almost constantly for about two years. A curettage had been performed elsewhere the previous year with only very temporary relief of symptoms. The diagnosis at that time was reported to be endometrial hyperplasia. The patient was curetted and advised to have a hysterectomy because of the pseudomalignant pattern of the endometrium (Fig. 4, A). She refused operation, and was not free of symptoms following her curettage so was placed on cyclic progesterogen therapy, 30 mg. a day of pregnenolone for seven days, as a palliative measure while she considered further treatment. Her response was satisfactory and the following month she again received cyclic progesterogen therapy. An endometrial biopsy was taken after treatment the second month and marked squamous metaplasia was found (Fig. 4, B). Hysterectomy was again advised and this time the recommendation was accepted. At operation, the uterine lining appeared to be compatible grossly with benign polypoid hyperplasia but, on microscopic examination, a small area of hyperactivity was seen in the region of the right cornu (Fig. 4, C) which under higher power was diagnosed as adenoma malignum (Fig. 4, D). There was no invasion of the myometrium and the patient is living and well three years postoperatively.

Interval Nonsecretory Endometrium.—Seventeen cases, or 16 per cent, showed interval nonsecretory endometrium on the initial curettage. Subsequent curettings on five of these women showed hyperplasia or chronic endometritis (Table IV).



Fig. 2.—Curettings from a patient during a period of remission taken six months after the last therapy. Patient had been having regular menses. Photomicrograph. Low power.

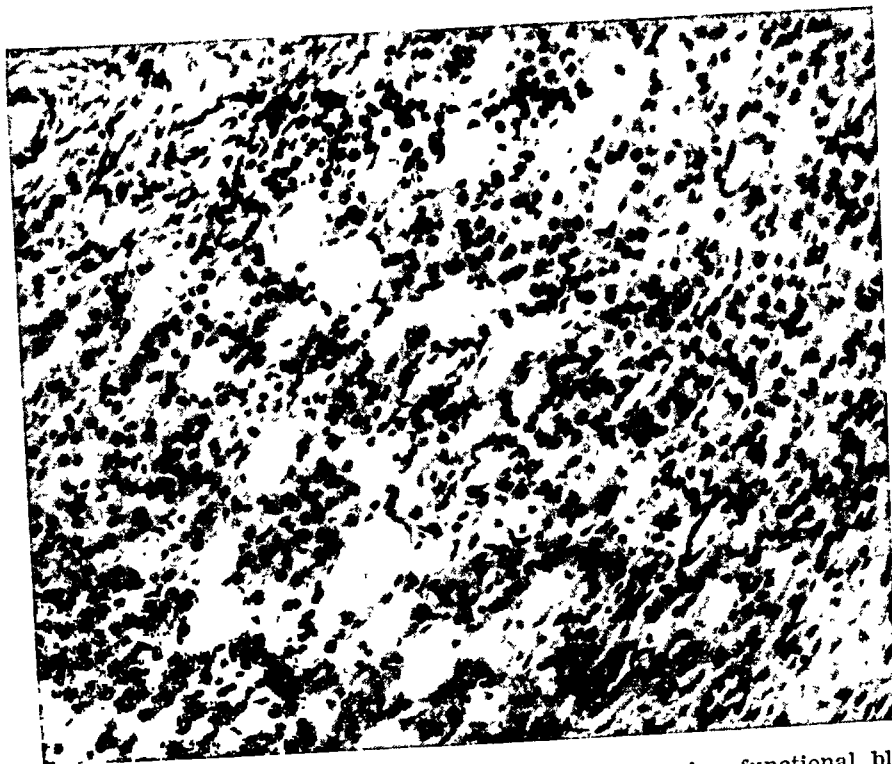


Fig. 3.—Tissue found in the hilum of the ovary of patient having functional bleeding which was irresponsive to progesterogenic therapy. Photomicrograph. Low power.

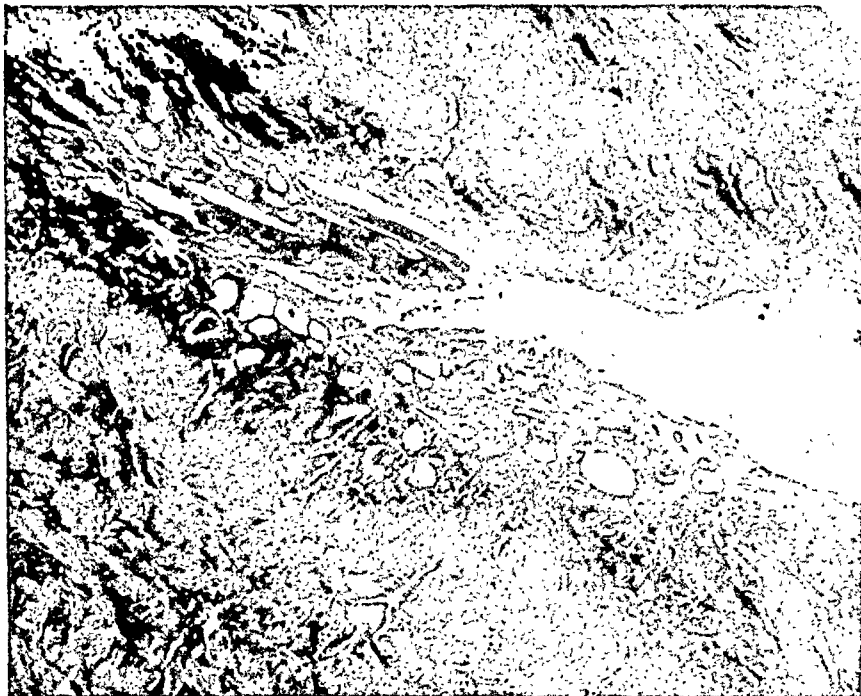


Fig. 4, C.—Endometrial lining obtained at hysterectomy. There is a small, extremely cellular adenomatous area in the upper right corner. Photomicrograph. Low power.



Fig. 4, D.—A high power photomicrograph of the adenomatous area showing adenomaligntum.



Fig. 4, A.—Curettings from E. G. obtained before therapy. There are areas suggestive of metaplasia and a marked decrease in the stromatogenous elements. Photomicrograph. Low power.

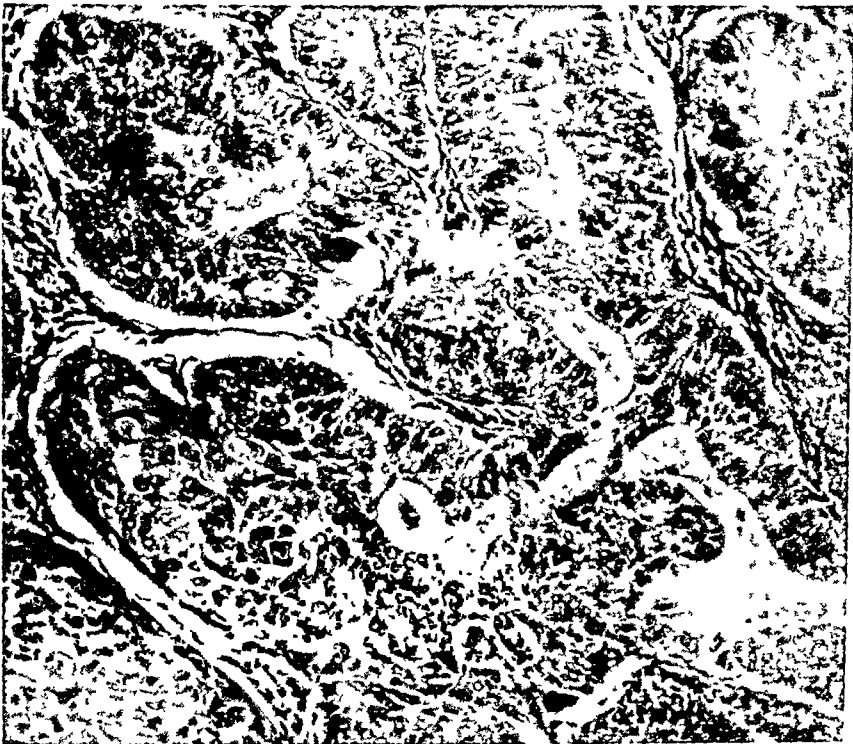


Fig. 4, B.—Curettings obtained after second month of cyclic progestogenic therapy. There is marked squamous metaplasia. Photomicrograph. High power.

Secretory Endometrium.—Among those referred to the special clinic, there were thirteen patients who initially, or without therapy, showed secretory endometrium. There was a striking difference in the symptomatology of these patients, as the complaint was prolonged or profuse menses with intermenstrual spotting in nine cases, while only four of the thirteen women had any irregularity of the menstrual interval. After a period of study, a number of these patients were eventually shown not to have true or uncomplicated cases of functional uterine bleeding (Table VII). One had had profuse, prolonged menses over a period of four years and, finally, at hysterectomy, proved to have a submucous myoma and adenomyosis. Another developed palpable endometriosis while under observation. Two had associated pelvic inflammatory disease and acute cervicitis with positive Neisserian cultures, while an additional two had parametritis following abortions. All four patients with inflammatory processes were successfully treated by chemotherapy, douches, and bed rest. One of these is now pregnant after a two-year history of profuse bleeding and sterility.

Seven patients had functional bleeding in the light of the original definition, e.g., there was no abnormality in the uterus; however, two of these had thrombocytopenic purpura and one had hypertension. The remaining four seemed to have functional disturbances representing abnormalities of the corpus luteum function. These latter patients had a disturbance of the menstrual interval represented by prolonged, irregular cycles followed by profuse, prolonged menses. Two were women who had exhibited such disturbances throughout their menstrual lives, and probably had true endocrine dyscrasias. The other two had a sudden onset of symptoms correlated with acute psychiatric disturbances. All four women had small ovarian cysts at the time of curettage, and the first two patients had been temporarily relieved of symptoms elsewhere by operative removal of ovarian cysts. Although it is expected that these were probably corpus luteum cysts, unfortunately, no pathologic report is available to corroborate the diagnosis.

Six of the thirteen patients (Table VII) were treated unsuccessfully with progesterone. It was believed that such an unsuccessful result was to be expected, as surely there is no rationale for such therapy.

TABLE VII. FINAL DIAGNOSIS AND ANALYSIS OF CASES SHOWING SECRETORY ENDOMETRIUM SEEN IN THE SPECIAL FUNCTIONAL BLEEDING CLINIC

FINAL DIAGNOSIS	NO. CASES	DISTURBED MENSTRUAL INTERVAL	PROGES- TERONE TREATED	SUCCESSFUL RESULTS
Thrombocytopenic purpura	2	0	1	0
Pelvic inflammatory disease and parametritis	4	0	2	0
Adenomyosis	1	0	1	0
Endometriosis	1	0	1	0
Hypertension	1	0	0	—
Corpus luteum cysts (?)	4	4	1	0
Totals	13	4	6	0

Discussion

From the present study, it was found that only about 17 per cent of the cases of functional uterine bleeding seen in the gynecologic out-patient department at the Johns Hopkins Hospital were severe enough or in the age group to require special treatment. The remaining 83 per cent were satisfactorily handled by simple curettage, or, if necessary, in the older age group, by hysterectomy or irradiation therapy.

Fifteen patients were judged suitable for progesterogen therapy. Thirteen had excellent results. Five of these have had no recurrence following discontinuation of cyclic progesterone. Of these five, three had no adjunctive treatment, and two had necessary dietary adjustments.

Two patients failed to respond to progesterogen therapy. One was a 24-year-old Negro woman who was thought to have typical functional bleeding but continued to have a bloody discharge throughout treatment. Pelvic inflammatory disease was suspected and the bleeding yielded to chemotherapy and douches. The second failure was in a 19-year-old obese patient who had a diagnosis of chronic endometritis on her second curettage. Because of a palpable enlargement of the right ovary, a laparotomy was performed and an enlarged ovary resected. Grossly no tumor was detected, but microscopically there was a diffuse collection of chromaffin-like cells in the hilum (Fig. 3). The patient has remained well following this operation and is now pregnant two years later.

Two patients were not treated with progesterone. Both were young girls, 12 and 16 years of age, in the first year of their menstrual life. Both responded to general hygienic measures consisting of improvement in eating, sleeping, and work habits.

The histories, symptoms, and clinical findings in this group of patients were identical with those found in the group with the diagnosis of endometrial hyperplasia.

Chronic Endometritis.—Three patients showed chronic endometritis when first curetted. Two had variations in patterns on subsequent curettages (Table IV). Only one patient received hormone therapy. This 22-year-old Negro woman had had irregular, excessive vaginal bleeding since her menarche, 9 years before. She received two courses of progesterogen therapy, and had a recurrence of symptoms six months after cessation of her primary therapy. Two years later she was asymptomatic, except for some irregularity in her menstrual interval. The second case was seen following her second curettage but did not return for therapy. The third patient had hypertension and was advised to have x-ray castration. She refused and was unimproved symptomatically when last seen five months after curettage.

Atrophic Endometrium.—Two cases of atrophic endometrium were studied. Both were young women, 19 and 21 years of age, who had had numerous curettages elsewhere. One had received a small dose of intrauterine radium. Bleeding was exsanguinating, in both cases necessitating repeated transfusions. Pregneninolone had been used in both cases elsewhere and was reputed to have been unsuccessful. Both were treated successfully by giving from 1 up to 3 mg. of stilbestrol a day for seventeen days, followed by a seven-day course of from 5 to 10 mg. of progesterone intramuscularly. Of these, the first patient had to leave the city, and had a recurrence of symptoms almost immediately after cessation of therapy. Intrauterine irradiation was used at that time. The second patient has been treated for five months, and is still having therapy. It will be noted that these cases were extremely severe, and that they did not receive a trial of oral progesterone in our clinic because of the story of failure elsewhere. It is, therefore, not definitely known how such patients would respond to oral medication for histories as given by patients are notoriously unreliable. It is also impossible to evaluate the use of estrogens in these cases because there is no control period. However, it seems that if estrogen were ever indicated, it would be in cases showing little or no endometrium.

The fact that 18 per cent of all cases treated (Table VI) became pregnant is a strong argument for perseverance with conservative therapy of functional bleeding.

Because we do not believe that cyclic progesterogen therapy is a specific cure for functional bleeding, all patients are investigated to determine if possible what the etiological factors underlying the condition might be. Thirty-three women in the present series had indications of a lowered thyroid function as judged by a basal metabolic rate below -5 or blood cholesterol above 250 mg. per cent. Twenty-three of these women apparently responded to therapy; the usual dosage being 1½ to 2 grains a day over a period of at least four months. Thirteen of the twenty-three women were also on special reducing diets. Ten patients were unresponsive to thyroid and three were unsatisfactorily followed. Fifteen women were successfully treated by diet alone; one mild diabetic patient falls into this group. Two patients with mild hyperthyroidism were treated by bed rest and Lugol's solution. A number of patients who have been judged as successfully treated had recurrences because of lapses in therapy but in each case they have responded satisfactorily again to treatment.

In the present series it was found that true cases of functional bleeding from secretory endometrium are rare. Of the thirteen cases, only four, or approximately 4 per cent of the total series, were finally selected as being uncomplicated functional disorders. These four had ovarian cysts, which were probably corpus luteum cysts, and showed disturbances of the menstrual interval as did all of the nonsecretory cases. It is interesting that there were two cases of thrombocytopenic purpura in the group, which stresses the importance of keeping the medical aspects of the disease well in mind.

Summary

1. During the past seven years, approximately 700 cases of functional bleeding have been seen in the gynecologic out-patient department of the Johns Hopkins Hospital. During this same period, 104 young women with severe symptoms have been selected from the general dispensary for referral to the special functional bleeding clinic. Thus, only about one case in seven was severe enough symptomatically or in the proper age group to require conservative therapy other than curettage.

2. When 104 cases of functional uterine bleeding were classified according to the endometrial diagnosis of the original curettings, 66 per cent were hyperplastic, 16 per cent interval nonsecretory, 12 per cent secretory, and the remaining 6 per cent were chronic endometritis and atrophic types.

3. A total of 234 curettements was done on these 104 patients. Sixty-three per cent of the repeated curettages performed for a recurrence of symptoms showed no change in the endometrial pattern. Of the remaining 36 per cent of patients who showed a variation in pattern, none of the untreated varied from the nonsecretory type to secretory.

It was further noted that of the 104 cases of functional bleeding referred during the past seven years for special consideration in the functional bleeding clinic, only seventy-one, or 69 per cent, were thought suitable for endocrine therapy.

A total of 234 curettages were performed on the same 104 patients. The initial diagnosis was hyperplasia in 66 per cent, interval nonsecretory in 16 per cent, secretory in 12 per cent, and other patterns (chronic endometritis, atrophic) in 6 per cent. Thirty-seven per cent of the cases showed no change in diagnosis on subsequent curettages. In the remaining 63 per cent, variations in patterns occurred. These were apparently mutually interchangeable among the nonsecretory groups. Patients with an initial diagnosis of secretory endometrium showed variations in pattern in subsequent curettements, but these were compatible with the day of the cycle at which the curettement was performed.

As the endometrial patterns were interchangeable among the nonsecretory groups, it might be assumed that the response to therapy would be uniform. This, indeed, seems to be the case, for if the patient with an ovarian neoplasm is excluded, there has not been a single failure of progesterogen therapy among the patients bleeding from a nonsecretory type of endometrium. The patients having an associated gonorrheal cervicitis should be excluded as unsuitable for treatment. The cases showing secretory endometrium, however, seem to have a different etiology and might be expected to respond differently to therapy. Not one case with secretory endometrial bleeding has been successfully treated by progesterone.

In the present series of cases, cyclic oral progesterogen therapy has been used almost entirely. In two cases having atrophic endometrium, from 3 to 5 mg. of stilbestrol were given daily for two weeks before beginning progesterogen therapy. These two patients and an additional three showing interval nonsecretory and hyperplastic endometrium seemed to respond better to intramuscular progesterone than to oral proginolone. Therefore, in severe cases, especially in those with low hemoglobin, when it is important to control the symptoms as rapidly as possible, it is probably wiser to use the drug intramuscularly, at least in the first course of therapy. Thus, the variations in response to therapy which may be expected to occur with any oral medication can be avoided.

In using progesterogen therapy, two things should be emphasized; first, it is not a hemostatic drug, and bleeding does not cease until a week after progesterone withdrawal; second, it probably does not cure the underlying condition or conditions but only relieves the symptoms; therefore, recurrences are to be expected. In the present series, 57 per cent of the cases successfully treated had a return of symptoms within six months to two years after cessation of therapy. Recurrences have been successfully treated by another series of cyclic progesterogen therapy.

Although we have regarded progesterogen therapy as palliative only, it is interesting to note that about 50 per cent of the patients who had no recurrence of symptoms after the initial course of progesterone had no adjunctive therapy.

FACTORS INFLUENCING THE RAT OVARY HYPEREMIA REACTION AS A TEST FOR PREGNANCY

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THE present study was undertaken to evaluate the controversial factors which have been found to influence the accuracy of the rat ovary hyperemia reaction, with particular regard to the diagnosis of pregnancy. The differences in accuracy between the favorable^{3, 7, 9-17, 4} and unfavorable reports^{2, 5, 8, 1} were considered to be due to variances in test procedure. In the favorable reports, as well, the test routine varied and there were diverse opinions on the effect of the various factors in the test material and procedure on the accuracy of the reaction.

Procedure and Methods

Studies were performed on a series of 517 urine specimens sent to the Endocrine Laboratories of the Jefferson Hospital for the two-hour rat ovary hyperemia pregnancy test. The test procedure basically was as follows: immature albino rats of a Wistar strain, 26 to 32 days old and 45 to 60 Gm. in weight, were injected intraperitoneally with 2 c.c. of urine, were killed in two hours by ether asphyxiation, and autopsied. The rat ovary hyperemia reaction was negative if the ovaries were pale or pinkish. The reaction or test was positive if one or more ovaries were hyperemic, being light to dark crimson in color, without consideration of ovarian enlargement or follicle changes.

The investigation included such factors in the test animals as age, weight, strain, and number; the factors in the urine specimen, as albumin, pH, temperature, hormones, cloudiness, specific gravity, and bacteria; the factors in the administration of the urine, as injection site, number of injections, and dosage; the factors in asphyxiation as asphyxiating agent, optimum time for asphyxiation; and the factors in the autopsy as optimum time for autopsy after asphyxiation, autopsy technique, color intensity, and reading. For comparative studies, the minimal effective dosage* (M.E.D.) of chorionic gonadotrophin† for the hyperemia reaction at two hours was determined and found to be 0.6 International Unit. Positive reactions were present in 76 per cent of the 50 rats injected with this dosage which paralleled the reaction accuracy (77 per cent) noted by us with normal pregnancy urines at two hours. More than 2,000 rats were used for this investigation.

Results and Discussion

The Test Animals.—The weights in the favorable reports were either of a wide range, 30 to 80 Gm.,¹¹ a limited range, 35 to 40 Gm.,¹⁴ or specific, 50 Gm.⁷ The ages were from 18 to 55 days. In this series, the best weight was found to be 45 to 60 Gm., and the best age from 26 to 32 days (Table I).

*The minimal effective dosages were considered to be the smallest amount to produce positive ovary hyperemia reactions in approximately 75 per cent of five or more rats.

†A. P. L. (Ayerst, McKenna, and Harrison).

The patients showing endometrial hyperplasia and other types of non secretory endometrium were clinically similar and on subsequent curettages showed the endometrial patterns to be mutually interchangeable. For this reason, no differentiation has been made between these groups in the evaluation of therapy.

4. Seventy-four of the 91 patients showing nonsecretory endometrium were considered suitable for cyclic progesterogen therapy in that they constituted a group of young women with severe symptoms which did not respond to other forms of treatment. In 72 cases, the bleeding symptoms were satisfactorily controlled. A patient with an ovarian neoplasm and another with gonorrheal cervicitis and an associated pelvic inflammatory disease failed to respond to therapy. Thirty-one patients had no recurrence of symptoms following the initial three-month cyclic course of medication. Sixteen of these thirty-one patients had no adjunctive therapy. Recurrences which occurred in forty patients were successfully treated again with progesterone.

5. Oral proginolone has been as satisfactory as intramuscular progesterone in the present series, in approximately 90 per cent of the patients.

6. Estrogen has been used in conjunction with progesterone only in the two cases of bleeding associated with an atrophic type of endometrium.

7. There were thirteen cases showing secretory endometrium and originally considered to be truly functional in type. Of these, however, only four proved to have uncomplicated functional bleeding. These cases had a disturbance in the menstrual interval. In the other nine cases there were prolonged, profuse, but regular menses, although some of these had spotting during the menstrual interval. Six patients in this group showing secretory endometrium were treated with progesterone and none responded to therapy. It has been assumed, therefore, that although progesterogen therapy is excellent in functional bleeding associated with nonsecretory endometrium, it is unsatisfactory in those patients who have abnormal bleeding associated with secretory endometrial patterns.

We wish to express our appreciation to Roche Organon, Inc. for supplying us with the Progestoral necessary for this study.

References

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2. Jones, H. W.: *AM. J. OBST. & GYNIC.* 35: 64, 1938.

TABLE IV. EFFECT OF ALBUMIN IN NONPREGNANCY URINE UPON THE RAT OVARIAN HYPEREMIA REACTION

AMOUNT ALBUMIN*	NO. URINE SPECIMENS	CHORIONIC GONADOTROPHIN (I.U.)	NO. RATS	NEGATIVE REACTION
0	2	0	10	10
1	4	0	8	8
2	1	0	2	2
4	10	0	20	20
4	4	0.3	5	5

*Grade 1 plus to 4 plus by the Exton method.

A neutral or acid urine has been recommended for injection.^{9, 14} In this study, pregnancy urines or the M.E.D. of chorionic gonadotrophin were injected with an adjusted pH of 5.0 or 7.0. The ovarian reaction accuracies were similar (Table V).

TABLE V. EFFECT OF pH OF PREGNANCY URINE AND CHORIONIC GONADOTROPHIN ON THE ACCURACY OF THE RAT OVARY HYPEREMIA REACTION

pH	NO. RATS INJECTED WITH PREGNANCY URINES	NO. RATS INJECTED WITH 0.6 I.U. CHORIONIC GONADOTROPHIN*	FALSE NEGATIVE REACTIONS
5.0	194	-	26
	-	10	3
7.0	194	-	29
	-	10	3

*Minimal Effective Dosage—which was that amount which produced positive rat ovary hyperemia reactions in approximately 75 per cent of five or more rats.

It has been suggested that the urine be injected at room temperature⁷ or after heating to a temperature of 35° C. or 38° C.⁹ In this study, the urines of pregnant and nonpregnant women were injected at 36° C., 12° C., and room temperature while the M.E.D. of chorionic gonadotrophin was injected at 36° C. and 12° C. (Table VI). There was no notable variance in the accuracy of ovarian reaction. At 36° C. there was a slight increase in fluid retention in the abdominal cavity.

TABLE VI. EFFECT OF TEMPERATURE OF URINE AND CHORIONIC GONADOTROPHIN ON THE RAT OVARY HYPEREMIA REACTION AND URINE ABSORPTION

TEMPERATURE DEGREES C.	NUMBER URINES*	NUMBER RATS	FALSE NEGATIVE REACTIONS	FREE FLUID IN ABDOMINAL CAVITY			
				NONE	SLIGHT	MODERATE	MARKED
36	11	11	2	4	2	3	2
12	11	11	1	8	1	2	0
Room	11	11	1	6	3	2	0
36	Chorionic Gonadotrophin 0.6 I.U.†	6	1	6	0	0	0
12		6	1	6	0	0	0

*Six pregnancy and five non-pregnancy urines.

†Minimal effective dosage.

Rejection^{10, 14} or detoxification⁹ of urines contaminated with bacteria has been considered necessary. In this study, the percentage of toxic reactions was 0.8 after the injection of 2 c.c. of urine and 21.7 with 5 c.c. of urine

TABLE I. RELATIONSHIP OF WEIGHTS OF RATS TO THE ACCURACY OF THE RAT OVARY HYPEREMIA REACTION

WEIGHT OF RATS (GM.)	NO. OF PREGNANCY URINES	NO. OF RATS	NO. OF FALSE NEGATIVE REACTIONS	ACCURACY PER CENT
31-35	32	64	23	74.0
36-45	83	166	39	76.5
46-50	168	336	45	81.0

In the recent favorable reports, one¹⁴ or two^{7, 11, 14} rats have been used. In this study three rats per test were necessary for the greatest accuracy (Table II).

TABLE II. RELATIONSHIP OF THE NUMBER OF RATS USED PER TEST TO THE ACCURACY OF THE RAT OVARY PREGNANCY TEST

NO. RATS PER TEST	NO. PREGNANCY URINES	NO. FALSE NEGATIVE TESTS	ACCURACY PER CENT
1	56	10	82.2
2	33	2	94.0
3	15*	0	100.0

*Ectopic pregnancies.

Preparation of the Urine Specimen.—The amount of urine injected by others depended upon the specific gravity,¹⁰ was increased for daytime specimens,^{7, 9, 11} or the urine was rejected if the specific gravity was less than 1.010¹⁴ or 1.012.² Filtration of all urines¹⁰ or of cloudy urines alone,⁹ the use of only clear urines,¹⁴ or centrifuging of urines to remove sediment⁷ have been advocated as well. In this study there was a slight increase in the number of false negative reactions after the use of clouded urines with a high specific gravity which apparently retarded urine absorption (Table III). Of note in our series were two cases of pregnancy in which the urine specific gravities were 1.003 and 1.004. One was a ruptured ectopic pregnancy and the other was an early normal pregnancy in which the urine specimen was collected five days after the expected date of the first missed menses. The ovarian reactions were strongly positive in the four animals injected.

TABLE III. RELATIONSHIP OF SPECIFIC GRAVITY OF PREGNANCY URINES TO THE ACCURACY OF THE RAT OVARY HYPEREMIA REACTION AND PREGNANCY TEST

SPECIFIC GRAVITY OF URINE	NO. PREGNANCY URINES	NO. RATS	FALSE-NEGATIVE REACTIONS	FALSE NEGATIVE TESTS
1.000-1.010	10	20	2	0
1.011-1.020	40	80	10	1
1.021-1.030	48	96	16	3
1.031-1.040	14	28	6	2

Kline¹⁰ reported that urines of nonpregnant patients with slight traces of albumin may cause doubtful reactions while Ramsey et al.¹⁴ urged that the urine be free of albumin. In this study, the urines of nonpregnant patients with one to four plus albumin were injected alone, while in another group of rats subminimal doses of chorionic gonadotrophin, 0.3 International Units, were added to the nonpregnant urines with four plus albumin (Table IV). The ovarian reactions were negative, being pale in color.

TABLE VIII. EFFECT OF SPECIFIC NONPREGNANT URINES AND URINE GONADOTROPHIN CONCENTRATES UPON THE RAT OVARY HYPEREMIA REACTION

DIAGNOSIS	URINE ^{1, 2}			URINE GONADOTROPHIN CONCENTRATE ^{1, 3}			GONADO- TROPHIN ASSAY (M.U. PER 24 HOURS)
	NUMBER OF CASES	REACTIONS		NUMBER OF CASES	REACTIONS		
		POSITIVE	NEGATIVE		POSITIVE	NEGATIVE	
Midcycle ⁴	20	0	40	12	27	22	12-196
Amenorrhea ⁵	10	0	20	5	0	10	102 to over 196
Fibroids	10	0	20	-	-	-	-
Postpartum ⁶	12	0	24	-	-	-	-

¹Two rats injected per specimen.²Two c.c. of a 12 or 24-hour specimen collected for gonadotrophin assay.³Two c.c. of the urine gonadotrophin extract (alcohol-ether-acetone extraction) dissolved in 12 c.c. of distilled water represented 1/24th of the total 24-hour output of gonadotrophins.⁴Midcycle time and ovulation determined by temperature chart and endometrial biopsy.⁵Menopause and primary ovarian deficiency.⁶Lactating. Ten days post partum.⁷Same patient. Unconcentrated urine was not injected. Pregnancy occurred during that menstrual cycle. Corpora hemorrhagica and lutea in mice injected for gonadotrophin assay which was over 196 M. U. per 24 hours.

Factors in the Administration of the Urine.—The amount of urine injected by the advocates of this test has varied from 2^{11, 17} to 10 c.c.⁷ Salmon and his group¹⁷ used from 1 to 8 c.c. without an appreciable effect in ovarian reaction accuracy. In this study, 2 c.c. of urine injected intraperitoneally were considered to be the optimum dose after the evaluation of the series of rat ovary hyperemic pregnancy cases in which 2 or 5 c.c. were injected (Table IX). The accuracy of the ovarian reactions was the same.

TABLE IX. RELATIONSHIP OF THE AMOUNT OF INJECTED PREGNANCY URINE TO THE ACCURACY OF THE RAT OVARY HYPEREMIA REACTION

AMOUNT (C.C.)	TYPE OF PREGNANCY	NUMBER OF RATS*	FALSE NEGATIVE	ACCURACY PER CENT	TOXIC REACTIONS
2.0 ^a	Normal	242	35	85.4	3
	Disturbed	110	26	77.0	
5.0 ^b	Normal	164	28	83.0	50 ^c
	Disturbed	66	16	76.0	

*Two rats injected with each urine. a. Intraperitoneally. b. 2 c.c. intraperitoneally. 3 c.c. subcutaneously. c. Not toxic in 2 c.c. doses.

Kupperman and Greenblatt¹¹ advised that 2 c.c. of urine be injected intraperitoneally in two divided doses to facilitate the absorption of urine and produce a sharper point. In this study, in 371 cases, 2 c.c. of urine were injected intraperitoneally in single and divided doses without a notable difference in ovarian reaction accuracy. This was corroborated when 2 c.c. of each of ten pregnant women's urine was injected into twenty rats in single and divided doses (Table X). With the latter urine absorption was slightly less.

TABLE X. EFFECT OF SINGLE AND DIVIDED INTRAPERITONEAL INJECTIONS OF PREGNANCY URINE UPON THE OVARY ABSORPTION AND HYPEREMIA REACTION

	NO. RATS	URINE IN ABDOMEN				POSITIVE REACTIONS		
		NONE	SLIGHT	MODERATE	MARKED	STRONG	MODERATE	WEAK
Single*	10	7	2	1	0	5	4	1
Divided†	10	5	3	2	0	4	4	2

*Two c.c. lower midabdomen.

†One c.c. into each of the right and left lower quadrants.

(Table IX). Though a number of the urines were contaminated with bacteria, the three urines which were toxic in 2 c.c. doses were free of bacteria but contained penicillin which had been given to the patient prophylactically.

Farris⁶ noted an occasional positive reaction after the injection of estrogens while Kline¹⁰ reported that estrogens in the urine of nonpregnant women may cause doubtful reactions. In this study, an aqueous suspension of estrone sulfate was injected into 10 rats in doses of 5,000 to 40,000 International units, while progesterone in an aqueous suspension* was injected into 8 rats in doses of 5 mg. All reactions were negative.

Kupperman and Greenblatt¹¹ indicated that the ovary hyperemia reaction is dependent upon the luteinizing or luteotrophic gonadotrophins and cannot be induced by the follicle-stimulating gonadotrophin. Farris⁶ found that ovary hyperemia was produced by pure anterior pituitary hormones as the follicle-stimulating hormone (McShan), the luteinizing hormone (Gurin), and the follicle-stimulating synergist (Schering). The ovarian hyperemia reaction was elicited in this study by the following gonadotrophins: sheep or horse pituitary, chorionic, lactogenic (luteotrophic), and pregnant mares' serum. The relative activity of each was noted (Table VII). In addition, Zondek et al.¹ and Farris^{5, 6} reported false positive rat ovary hyperemia pregnancy tests upon the injection of urines with a high content of follicle-stimulating hormone (menopause, fibroids, midinterval of the cycle of patients with normal menses). In this study, the two-hour rapid rat pregnancy test was performed with the urine of these types of cases and with the urines of lactating postpartum (tenth day) patients in which high levels of lactogenic hormone, and low levels of chorionic gonadotrophin may be expected (Table VIII). In the "midcycle" and amenorrhea cases, 2 c.c. of the urine gonadotrophin assay extract were also used. The reactions to the urines and gonadotrophin extracts were negative with one exception.

TABLE VII. MINIMAL EFFECTIVE AMOUNTS OF GONADOTROPHINS EVOKING THE RAT OVARY HYPEREMIA REACTION

GONADOTROPHIN	M.E.D. ¹
Whole pituitary	
Equine pituitary ²	0.3 R.U.
Gonadophysin ³	0.5 R.U.
Pituitary synergist ⁴	0.155 U.
Chorionic	
Korotrin ⁵	0.60 I.U.
Follutein ⁶	0.55 I.U.
Antuitrins ⁷	0.65 I.U.
A.P.L. ⁸	0.60 I.U.
Pregnant Mares' Serum	
Anteron ⁹	2.5 I.U.

¹Minimal effective dose. That amount which produced positive rat ovary hyperemia reactions in approximately 75 per cent of five or more rats.

²Squibb.

³Searle.

⁴Kindly furnished by Dr. Erwin Schwenk of Schering Corporation. Made from sheep pituitaries and is chiefly follicle-stimulating hormone with traces of luteinizing hormone.

⁵Winthrop.

⁶Squibb.

⁷Parke, Davis & Co.

⁸Ayerst, McKenna, and Harrison.

⁹Schering.

*Kindly furnished by Dr. Erwin Schwenk of Schering Corporation.

Asphyxiation.—In the various reports on the rapid rat pregnancy test, the optimum time for asphyxiation after injection has varied from two to thirty hours. Zondek et al.¹ reported the accuracy of the subcutaneous test to be greatest at twenty-four hours, least at two hours, and intermediate at six hours. Salmon and his group¹⁷ noted the six-hour subcutaneous test to be slightly more accurate than the two-hour test and to be more striking than the twelve and twenty-four hour tests. Others^{10, 14} found the six-hour test with subcutaneous injections to be the most reliable. Bunde² estimated the two-hour intraperitoneal test to be more accurate than the six-hour subcutaneous test, while Kupperman and Greenblatt¹¹ considered them to be equally accurate. Fried.⁵ in a small series, judged the two- and six-hour intraperitoneal tests to be equally accurate. It has been stated that tests can be read at thirty hours¹⁰ or thirty-six to forty-eight hours¹¹ after injection. The ovary hyperemia reaction with chorionic gonadotrophin is reported to begin in two hours and reach its peak in twenty-four hours.¹ In this study, in determining the optimum time for asphyxiation after injection, the minimal effective dosage of chorionic gonadotrophin was noted at various time levels (Fig. 1). The smallest M.E.D. was noted at three to six hours, which, therefore, were the times of maximum effect. The M.E.D. was slightly increased at one and one-quarter, two, nine, and twelve hours, and the accuracy with the pregnancy test may be about the same as at the times of maximum effect. However, before one and one-quarter and after twelve hours the results may be much less accurate with pregnancy urines of comparatively low gonadotrophin content, since the M.E.D. rose sharply at these time levels. The earliest time reaction was at ten minutes.

The asphyxiating agents recommended have been ether, illuminating gas, and chloroform. Ether as the asphyxiating agent was found to be very satisfactory since the hyperemic ovaries stood out in good contrast to the pale uteri and oviducts. Since illuminating gas causes a varying hyperemia of the tissues, due largely to the formation of carboxyhemoglobin, consideration was given this asphyxiating agent to increase the sharpness of the positive end point. In this study, ether and illuminating gas were used to asphyxiate the control rats as well as the animals injected with urines of menopausal women and nonpregnant normally menstruating women collected at the midcycle. The ovarian reactions of the rats asphyxiated with ether were "negative" while some "positive" reactions occurred after asphyxiation with illuminating gas (Table XI). Farris,⁵ who used illuminating gas, reported the two-hour rapid rat pregnancy test to be inaccurate because of the large number of false positive reactions in menopausal and normal nonpregnant women at the midinterval of the cycle. Salmon¹⁶ stated that illuminating gas in some parts of the country may cause a hyperemia of the rat ovary in which case the use of ether is advisable.

TABLE XI. HYPEREMIA EFFECT UPON THE OVARY PRODUCED BY ASPHYXIATING AGENTS

URINE*	ASPHYXIATING AGENTS			
	ETHER		ILLUMINATING GAS	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Menopausal†	0	12	6§	6
Midcycle‡	0	12	3§	9
Controls	0	3	3	0

*Two c.c. injected into each rat.

†Urine gonadotrophins, 102 to over 196 mouse units per 24 hours in the three patients.

‡Midcycle and ovulation determined by temperature chart. Urine gonadotrophin, 12 to 96 mouse units per 24 hours in the three patients.

§After two minutes three were pale negative, five were borderline negative pink, and one remained positive.

A particularly controversial point in the performance of the two-hour rat pregnancy test is the best route of injection, subcutaneous or intraperitoneal. Kupperman and Greenblatt¹¹ noted a 99.5 per cent accuracy with the intraperitoneal route and a 65 per cent accuracy with the subcutaneous avenue of injection. They were of the opinion that the high percentage of inaccurate results obtained by Zondek et al.¹ (31.5 per cent errors in normal pregnancy) and Farris⁵ were due to the use of the subcutaneous rather than the intraperitoneal route of injection. Salmon,¹⁶ however, reported a 95 per cent accuracy with the subcutaneous injection. In this study, the minimal ef-

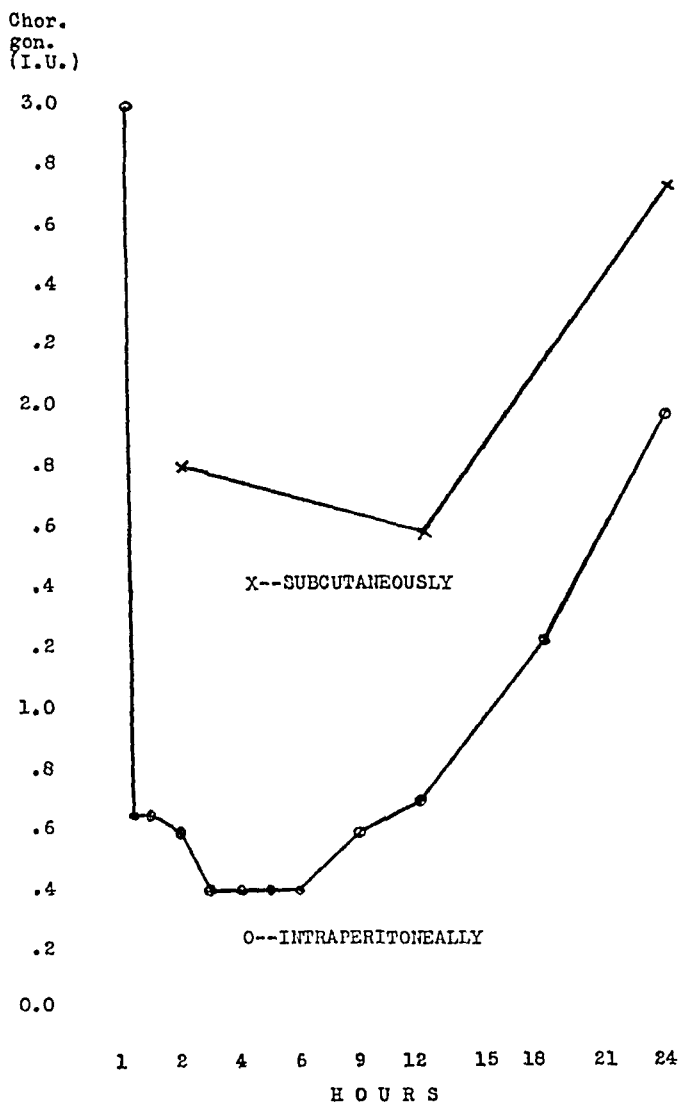


Fig. 1.—Minimal dosage* of chorionic gonadotrophin at various time levels on basis of rat ovary hyperemia reaction.

fective dosage of chorionic gonadotrophin injected subcutaneously and intraperitoneally was determined and compared at two, twelve, and twenty-four hours (Fig. 1). At these time levels, the subcutaneous doses were much higher than the corresponding intraperitoneal dosages. Moreover, when the minimal intraperitoneal dose of chorionic gonadotrophin at two hours, 0.6 International units, was injected into 12 rats intraperitoneally and 12 rats subcutaneously, positive ovarian hyperemia reactions were noted in 75 per cent of the former and 25 per cent of the latter.

in the two series. Three rats were used in a number of cases in the two-hour test while two rats were used in all of the three-hour tests. The two and three-hour rat tests were similar in accuracy (Table XII). Since the rapid rat pregnancy test has not been accepted by some as a routine laboratory test because of the large number of false negative reactions and lack of a sharp positive end point,^{2, 8, 1} the two procedures were also compared on this basis. The number of false negative reactions was less in the three-hour test than in the two-hour test (Table XII). Moreover, the end point of the positive reactions in the three-hour test was slightly more pronounced.

TABLE XII. COMPARISON OF PREGNANCY TESTS

PREGNANCY TEST	PREGNANCIES				NONPREGNANT		FALSE NEG. REACTIONS
	NORMAL		DISTURBED				
	POS.	NEG.	POS.	NEG.	POS.	NEG.	
Three-hour rat ovary hyper- emia	81	3	20	10 ²	1	84	37 (16%)
Two-hour rat ovary hyper- emia	83	4	24	11	0	78	60 (27%)
Friedman rabbit	114	5	26	26†	3	159	—

*One false negative.
†Four false negative.

The number of false negative reactions, though lowered, still was high in the three-hour test and apparently was not due to factors in the test performance. From the data in a series of 316 cases, it was apparent that approximately 95 per cent of the negative and doubtful reactions in pregnancy cases were due to individual animal variation. That is, there was variation in ability to absorb the injected urine or, if absorption occurred, the ability to react to the absorbed gonadotrophin. For corroboration, the following experiments were performed. Two c.c. of urine of each of two pregnant women were injected intraperitoneally into each of two rats. Each urine evoked one positive and one negative reaction. There was no urine in the abdominal cavities of two rats of which one was positive and the other negative. The latter was considered as a "nonreactor." Of the other two rats, 0.4 c.c. of urine was present in the abdominal cavity of the positively reacting rat and 1.3 c.c. in the negative rat. The 1.3 c.c. of urine were aspirated and were injected intraperitoneally into another rat. A strong positive reaction resulted. The latter negative reaction was attributed to poor absorption of the urine. This study was repeated with other urines with similar results. The largest number (90 per cent approximately) of the false negative reactions in a series of 316 cases with the modified technique was due to "nonreacting" rats, since the urine was completely absorbed. Further investigation is necessary to decrease the number of false negative reactions and to increase the sharpness of the positive end point.

Summary and Conclusions

Differences in the test procedure of the rapid rat pregnancy test have been considered the basis for the disparity in accuracy between the favorable and unfavorable reports; the inaccuracies in the latter were largely due to false negative reactions. Moreover, there has been a difference in opinion on the effects of certain factors in the urine, such as albumin, pH, temperature, hormones, cloudiness, specific gravity, and bacteria, as well as

Autopsy.—Autopsy has been advised immediately after asphyxiation and also five minutes after the animals are placed in the death chamber.^{10, 14, 17} In this study, five of seven rats were injected intraperitoneally with 0.6 to 20.0 International units of chronic gonadotrophin. After two hours the rats were anesthetized with ether and the ovaries were immediately exposed. The normally pink color of the ovaries was increased in the injected, anesthetized rats, dependent upon the dose of injected chorionic gonadotrophin. The ovaries were then observed during and after ether asphyxiation. As the point of asphyxiation approached, all ovaries blanched and at death were completely pale. The control ovaries remained pale. In the injected rats the time necessary for the ovarian color change from "death paleness" to a positive crimson was dependent upon the dose of chorionic gonadotrophin and the final degree of color, ranging from three minutes for the minimal to one minute for the larger amounts of chorionic gonadotrophin.

The technique of autopsy is important. Bleeding in the region of the ovaries has been considered a significant factor since it may cloud the reading.^{11, 17} In this study, three rats were injected with 1 International unit of chorionic gonadotrophin, asphyxiated with ether in two hours, and autopsied. The ovarian reactions were positive. A small incision in the liver or abdominal blood vessels caused moderate bleeding and incited almost immediate blanching of the hyperemic ovaries. Irritation of the ovaries during inspection also blanched hyperemic ovaries. The amount of irritation necessary was directly proportional to the degree of color.

To increase the color intensity at autopsy it has been advised that traction be applied to the uterus and ovary¹⁰ or that the ovaries in situ be exposed to the atmosphere for five minutes.¹⁶ In this investigation, traction to the uterus either increased or decreased the color intensity, while exposure to air intensified the color of doubtful and positive reaction. In 316 cases, five doubtful reactions were intensified to weak positive reactions after five minutes of exposure. Since three of the five rats had been injected with urines of nonpregnant women, three reactions were false positives. Kline¹⁰ recommended immediate reading of the ovaries after autopsy since exposure may intensify the color of the ovaries and may add to the confusion in borderline cases.

The necessary features of a positive rat ovary hyperemia reaction as a test for pregnancy have been variously reported. In 4 per cent of the positive reactions only the left of the two ovaries was hyperemic. The left ovary frequently was more hyperemic than the right ovary. Enlargement of the ovary at two hours was infrequent and was not essential for a positive reading as considered in reports on the six hour and other tests. Hyperemia of the follicles alone was not sufficient for a positive reading. In a few cases, after the injection of urine from nonpregnant women or of subminimal doses of chorionic gonadotrophin, or after the use of illuminating gas, a borderline positive or a doubtful reaction was noted which faded within two minutes to a negative reaction.

Comparison of the Two-Hour and Three-Hour Tests.—A three-hour rapid rat ovary hyperemia pregnancy test was performed by the technique evolved by this study on each of 200 specimens of urine sent to the Endocrine Laboratory of the Jefferson Hospital by 200 ward, clinic, and private cases for a rapid rat pregnancy test. The results were compared on the basis of ultimate clinical diagnosis and Friedman tests with those of a reported series of 200 two-hour rat pregnancy tests⁸ in which the technique of test performance was that advised by Kupperman and Greenblatt.¹¹ The two techniques varied in time, number of injections, autopsy routine, and specific weight and ages of the test animals. The number and types of pregnancy cases were the same

PRIMARY AND SECONDARY SPONTANEOUS HABITUAL ABORTION

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HABITUAL abortion is a disturbing obstetric problem with an obscure etiology. Many investigators have employed prophylactic therapy with this and that vitamin, hormone, and method of treatment and have drawn conclusions regarding the etiology from the results of treatment. It has been difficult to comprehend the good results obtained by the empirical use of only one agent or mode of therapy. Perhaps additional measures were employed unwittingly and not appraised statistically. There has been no general agreement as to the definition of habitual abortion and some studies include patients who have had only one or two abortions. Could faulty selection of patients be responsible for the high percentage of successful pregnancies irrespective of the treatment employed? The present study was undertaken in 1940 against this background. It has several objectives: first, to define habitual abortion; second, to determine the incidence; third, to detect as many of the contributing factors, defects, and deficiencies as possible; and, finally, to evaluate the results obtained by correcting these conditions.

Definitions

An abortion is defined for the purpose of this study as a pregnancy ending at or before the twenty-second week of gestation and resulting in a fetus weighing 500 Gm. or less.

"Primary habitual abortion" is used to classify obstetric patients who have had three or more consecutive spontaneous abortions beginning with the first pregnancy.

"Secondary habitual abortion" designates those who have had three or more consecutive spontaneous abortions following delivery of one or more immature, premature, or full-term infants.

The definition of abortion given above was prompted by the following circumstances:

1. Consideration of fetuses on the basis of weight and duration of pregnancy has provided our Pathological Laboratory with a suitable description of an abortus.

2. In keeping with the Clinic policy of regarding a premature infant as weighing from 1,501 to 2,500 Gm., and a full-term infant as weighing over 2,500 Gm., it seemed proper to classify infants weighing from 501 to 1,500 Gm. as immature, and fetuses weighing 500 grams and less as abortuses.

3. The *Quarterly Bulletin of the New York City Department of Health* states that twenty cities require registration of stillbirths having twenty-two weeks or more gestation, while the United States Public Health Service bases its stillbirth statistics on a uterogestation of twenty weeks and over.

*Died May 2, 1948.

details of technique, such as injection site, dosage, number of injections, asphyxiating agent, optimum asphyxiation time, autopsy technique, and reading. These controversial factors were evaluated in this investigation in order to develop a test procedure which offered the maximum accuracy. This was done on a consecutive series of 517 urine specimens.

The technique found to be most satisfactory was as follows: Three 26- to 32-day-old, 45 to 60 Gm., female albino rats of the Wistar strain are used. Two c.c. of an unaltered urine, except for filtration if cloudiness is present, are injected intraperitoneally in a single dose. The rats are asphyxiated in three hours (not later than six) with ether preferable to illuminating gas as the asphyxiating agent. Autopsy is performed about three minutes after the death of the animals with particular care to avoid hemorrhage and ovarian irritation. The ovaries are examined immediately. A satisfactory end point is the presence of a distinct ovarian hyperemia, light to dark crimson in color as compared to pale or pinkish controls, in one or more of the ovaries examined, without regard to the color of individual follicles or ovarian enlargement. The results with this three-hour rapid rat pregnancy test were favorable. Although the two- and three-hour rat pregnancy tests were approximately similar in accuracy (96.7 and 96.5 per cent, respectively) the number of animals giving false negative reactions in the three-hour test was decreased (from 27 to 16 per cent of rats injected with pregnancy urines). The other major difficulty which had been encountered in the rapid rat pregnancy test was the lack of a sharp positive end point, which too was improved slightly with the three-hour test. Further investigation is necessary to decrease the number of false negative reactions and to increase the sharpness of the positive end point.

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TABLE II. PRIMARY HABITUAL ABORTION. OBSTETRICAL PERFORMANCE BEFORE AND AFTER CLASSIFICATION REGARDLESS OF THERAPY

	ABORTION		IMMATURE		PREMATURE		FULL TERM		TOTAL
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
Before	369	100.0	0		0		0		369
After	142	47.3	14		9		135	45	300
Total (uncorrected) performance	511	76.5	14	2.1	9	1.3	135	20.1	669

TABLE III. SECONDARY HABITUAL ABORTION. OBSTETRICAL PERFORMANCE BEFORE AND AFTER CLASSIFICATION REGARDLESS OF THERAPY

	ABORTION		IMMATURE		PREMATURE		FULL TERM		TOTAL
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
Before	295	62.3	0		9		169	35.7	473
After	95	46.1	3		8		100	48.5	206
Total (uncorrected) performance	390	57.4	3	0.5	17	2.5	269	39.6	679

A part of this study is devoted to an evaluation of results with treatment; therefore, it is necessary to determine the obstetrical outcome without treatment. This was done for each pregnancy *after* classification as shown in Tables IV and V. The total average abortion rate does not vary significantly from any of the individual pregnancies and was 65.0 per cent and 46.5 per cent for the two groups, respectively, with a full-term salvage rate of 26.4 per cent and 47.7 per cent. Full-term expectancy was somewhat better in the secondary group, which must be taken into consideration when evaluating results from any method of therapy. It is realized that a parallel series with and without treatment would be more systematic. However, Tables IV and V will be used as controls and will be referred to again as Type I therapy in Tables X and XI.

TABLE IV. PRIMARY HABITUAL ABORTION. OBSTETRICAL HISTORY AFTER CLASSIFICATION ACCORDING TO PREGNANCY WITHOUT THERAPY

PREGNANCY SEQUENCE	ABORTION		IMMATURE		PREMATURE		FULL TERM		TOTAL
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
First	48	61.5	6		3		21	26.9	78
Second	35	67.3	2		2		13	25.0	52
Third	16	66.6	2		—		6	37.5	24
Fourth	11	84.6	—		—		2	15.3	13
Fifth	9	66.6	—		1		2	22.2	9
Sixth and Over	7	53.8	—		—		6	47.2	13
Total (uncorrected) performance	123	65.0	10	5.3	6	3.1	50	26.4	189

TABLE V. SECONDARY HABITUAL ABORTION. OBSTETRICAL HISTORY AFTER CLASSIFICATION ACCORDING TO PREGNANCY WITHOUT THERAPY

PREGNANCY SEQUENCE	ABORTION		IMMATURE		PREMATURE		FULL TERM		TOTAL
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	
First	38	53.5	1		5		27	38.0	71
Second	17	44.7	1		1		19	50.0	38
Third	6	35.2	—		1		10	58.8	17
Fourth	3	30.0	—		—		7	70.0	10
Fifth	2	28.4	—		—		5	71.6	7
Sixth and Over	9	50.0	—		—		9	50.0	18
Total (uncorrected) performance	75	46.5	2	1.2	7	4.3	77	47.7	161

4. Streeter has shown that a gestation of twenty-two weeks produces a fetus weighing approximately 500 Gm.

5. No fetus weighing less than 500 Gm. has ever survived at the New York Hospital. However, according to Levine, there have been 32 survivals in infants weighing between 501 and 1,000 Gm.

It would appear from this evidence that the time-honored practice of considering premature labors of 28 weeks or less as a miscarriage, or an abortion, is in need of downward revision. These infants have survived and become classified as "living abortions," a rather undesirable term. Accordingly, in keeping with what has been said above, a practical classification of infants on the basis of weight and duration of pregnancy at the time of delivery is presented herewith:

CLASSIFICATION OF INFANTS ACCORDING TO WEIGHT AND DURATION OF PREGNANCY
AT THE TIME OF DELIVERY

CLASSIFICATION	BIRTH WEIGHT (GM.)	DURATION OF PREGNANCY (WEEKS)
Abortus	0-500	0-22
Immature	501-1,500	22-30
Premature	1,501-2,500	30-36
Full Term	2,501 and over	36-40

Present Study

Incidence.—This study covers a 15-year period (1933 to 1947) during which time 56,803 pregnancies were cared for at the Woman's Clinic of the New York Hospital. Statistical tables are offered telling a tale not always referred to in the text. Table I shows that 123 patients with primary habitual abortion were treated in 189 pregnancies, giving an incidence of 1:300. Sixteen did not return in a subsequent pregnancy. The highest number of consecutive abortions per patient was 11, the lowest 3, while the average number per patient was 4.2. There were 88 patients in the secondary abortion group who were studied in 115 pregnancies, giving an incidence of 1:493. The highest number of consecutive abortions was 10, the lowest 3, while the average per patient was 4.5. The definitions stated above were rigidly adhered to in the selection of patients for this study.

TABLE I. PRIMARY AND SECONDARY HABITUAL ABORTION

	TOTAL NUMBER OF PATIENTS	TOTAL NUMBER OF PREGNANCIES	TOTAL NUMBER OF PREG- NANCIES AT WOMAN'S CLINIC (1933-1947)		INCIDENCE
			HABITUAL ABORTION PATIENTS	TOTAL CLINIC POPULATION	
Primary abortion	123	669	189	56,803	1:300
Secondary abortion	88	679	115	56,803	1:493
Grand total	211	1348	304		

Obstetrical Performance.—The primary group had a total of 669 pregnancies; the secondary group had 679, making a grand total of 1,348 for analysis. The obstetrical history of each group *before* and *after* classification can be obtained at a glance from Tables II and III. The primary group had a total uncorrected abortion rate of 76.5 per cent and 57.4 per cent for the secondary group of patients. Both are considerably higher than the prevalent rate of 10 per cent for the entire clinic population. The immature, premature, and full-term salvage is also given in these tables; the latter is only 20.1 per cent and 39.6 per cent for the primary and secondary groups, respectively, whereas for the entire clinic it is over 80 per cent.

was poor to start with. Evidence of nutritional deficiency was found in many patients when specific laboratory tests were made. As will be emphasized in Table XIII, some of these patients manifested a hemorrhagic diathesis consisting of bleeding from the nose, gums, and anus, as well as facile bruising of the skin, in addition to vaginal bleeding. Threatened abortion had a higher incidence and may be indicative of a partial or marginal separation of the placenta, as in the case recently reported by Javert. Deficiency in vitamin C or K may be responsible for decidual bleeding which predisposes the patient to premature separation. Rutherford has found evidence of abnormal decidual bleeding in patients with threatened abortion by means of histological studies of decidual biopsies. Such a symptom-complex of bleeding is suggestive of deficiency in the anti-hemorrhagic vitamins C and K, which was partially confirmed by laboratory tests, especially with regard to "C."

Placenta previa had a much higher incidence in the habitual abortion in patients. Patients with threatened abortion were also found by Stander to have this complication with greater frequency. Recently, two uteri were observed following hysterectomy in the first trimester of pregnancy and one contained a central placenta previa and the other a marginal one. Ordinarily, placenta previa and premature separation of the placenta are seldom mentioned as causes for spontaneous abortion.

The data on premature rupture of the membranes are incomplete. Not infrequently, these patients have a leakage of fluid per vaginam in the fourth or fifth month of gestation. One can often obtain a history of prior intercourse under such circumstances. Accordingly, complete abstinence from coitus during the entire pregnancy has been part of the treatment. Coitus may also result in stimulation of uterine contractions and be undesirable for that reason.

TABLE VIII. OBSTETRIC COMPLICATIONS IN PATIENTS WITH PRIMARY AND SECONDARY ABORTION

COMPLICATION	PRIMARY ABORTION		SECONDARY ABORTION		CONTROL
	NO.	PER CENT	NO.	PER CENT	
Total no. of pregnancies	189		115		56,803
Nausea and vomiting	166	87	70	60	33.0 per cent
Toxemia of pregnancy	13	7	11	9	5.0 per cent
Threatened abortion	28	15	8	7	0.9 per cent
Placenta previa	8	4	2	2	0.3 per cent
Premature rupture membranes	10	5	6	5	30.0 per cent

Gynecological Complications.—It seemed pertinent to consider the various kinds of gynecological disease because of a possible role in the pathogenesis of habitual abortion. A summary of the various conditions is presented in Table IX. Retroversion had a much higher incidence than in a control series of 100 parous and 100 nonparous women. Perhaps some of the patients had a spontaneous correction with or without the aid of the knee chest position. Correction of persistent retroversion has usually been accomplished by the combined technique described by Javert. When this gave unsatisfactory results, and when the uterus was adherent, a suspension operation was performed, and other complications were also corrected at the same time. Two patients developed primary habitual abortion after uterine suspension and are therefore of special interest. Several patients had a myomectomy because of fibromyomas. The obstetrical results following uterine suspension and myomectomy were as follows:

	SUSPENSION		MYOMECTOMY	
	ABORTION	FULL TERM	ABORTION	FULL TERM
Primary habitual abortion	2	7	2	5
Secondary habitual abortion	3	4	2	3
Total	5	11	4	8
Incidence (per cent)	31	69	33	66

Clinical and Laboratory Data.—A complete history, physical examination, and certain laboratory determinations were performed on each patient. The pertinent data are presented in Tables VI and VII. Control incidences obtained from annual reports, publications, and individual studies of the department, are provided as available for ready comparison. It is readily apparent that both the primary and secondary groups of habitual abortion patients had similar contributing factors, defects, and deficiencies. This confirmed a suspicion that no single cause was responsible and at the same time indicated that secondary abortion patients should receive more serious consideration. While they have already demonstrated ability to have one or more children and, therefore, have a better prognosis as to full-term expectancy without treatment than the primary group, it is even better with specific measures. However, this advantage is offset by a much higher infantile mortality rate, as will be shown in Table XIV. While dietary information is lacking for the entire series of patients, one finds evidence of improper nutrition in the incidence of anemia, vitamins C and K deficiency. Blood loss from recurrent abortion may explain some of the cases with anemia. More specific data in this regard were obtained from a study of a separate group of 33 primary abortion patients and are provided in Tables XII and XIII.

TABLE VI. CLINICAL DATA ON PATIENTS WITH PRIMARY AND SECONDARY HABITUAL ABORTION

DATA	PRIMARY ABORTION	SECONDARY ABORTION	CONTROL
No. of patients	123	88	--
Race: White	93 per cent	92 per cent	88 per cent
Negro	7 per cent	8 per cent	12 per cent
Average age	31 years	31 years	23 years
Elderly primiparas (Over 35 years)	25 per cent	--	8 per cent
Gynecologic complications	60 per cent	52 per cent	--
Medical complications	4 per cent	9 per cent	--
Second husband	3 per cent	1 per cent	--

TABLE VII. LABORATORY DATA ACCORDING TO NUMBER OF PREGNANCIES IN PRIMARY AND SECONDARY ABORTION

DATA	PRIMARY ABORTION NO.	PER CENT	SECONDARY ABORTION NO.	PER CENT	CONTROL
Number of pregnancies	189		115		56,803
Wassermann	(175)		(105)		
Positive		6		7	2.0 per cent
Hemoglobin below 70 per cent	(139)	15	(89)	17	7.0 per cent
Rh Factor:	(40)		(28)		
Positive		83		88	85.0 per cent
Negative		17		12	15.0 per cent
Basal metabolism:	(28)		(6)		
Minus value		65		50	--
Vitamin C concentration [*] (Below 0.5 mg. per cent)	(44)	55	(11)	45	50.0 per cent
Prothrombin concentration† (Below 70 per cent of normal)	(26)	47	(8)	22	15.0 per cent
Modified prothrombin test‡ (Below 70 per cent of normal)	(14)	0	(3)	0	1.0 per cent

(Figures in parentheses indicate number of patients studied.)

*Mindlin and Butler Technique.

†Warner, Brinkhous, and Smith.

‡Summerson-Bonsnes.

Obstetrical Complications.—The occurrence of the same complications of pregnancy in either group as shown in Table VIII is of obstetrical interest. Nausea and vomiting occurred frequently, and served to reduce the value of an adequate antepartum diet, and were more pernicious when the patient's nutrition

promising results in seven patients with secondary habitual abortion. Insufficient consideration had been given to this group on the erroneous assumption that they needed no special consideration inasmuch as they had already born a viable child. This accounts for the small number of patients in the secondary group.

TABLE X. PRIMARY HABITUAL ABORTION. OBSTETRICAL OUTCOME FOLLOWING VARIOUS TYPES OF TREATMENT COMPARED WITH CONTROL

THERAPY	NUMBER OF PREG- NANCIES	ABORTION		IMMATURE		PREMATURE		FULL TERM	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Type I (control) See Table IV	189	123	65.0	10	5.3	6	3.1	50	26.4
Type II	50	13	26.0	4		1		32	64.0
Type III	41	6	14.6	0		2		33	80.4
Total	280								

TABLE XI. SECONDARY HABITUAL ABORTION. OBSTETRICAL OUTCOME FOLLOWING VARIOUS TYPES OF TREATMENT COMPARED WITH CONTROL

THERAPY	NUMBER OF PREG- NANCIES	ABORTION		IMMATURE		PREMATURE		FULL TERM	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Type I (control) See Table V	161	75	46.5	2	1.2	7	4.3	77	47.7
Type II	41	19	46.3	1		1		20	47.5
Type III	7	0		0		0		7	100.0
Total	209								

Special Clinic

A special clinic was established in 1940 for the study of habitual abortion and for the standardization of management and treatment. The contemplated program was interrupted by World War II so that, finally, only 33 patients had been uniformly studied and treated in 41 pregnancies. Data on these patients have been presented in Tables X and XI. Additional information pertaining to them is provided in Tables XII and XIII. Multiple factors, defects, and deficiencies were diagnosed and treated. Occasionally, after an abortion, corrective measures were instituted before the next pregnancy. Urological examinations were performed on nine husbands and normal spermatozoa were found in all. Two patients remarried and went to term in the very next pregnancy with Type III treatment.

Gradually vitamin E and progesterone therapy were discontinued with the following results:

	NO. OF CASES	ABORTIONS	PREMATURE AND FULL TERM
With progesterone	21	2	19
Without progesterone	20	1	19
With vitamin E	28	6	22
Without vitamin E	13	2	11

Virtually the same results were obtained with vitamin E and progesterone as without them. This led to a withholding of vitamins C and K in certain patients with primary habitual abortion with the following results:

With vitamin C	41	6	35
Without vitamin C	2	2	—
With vitamin K	33	7	26
Without vitamin K	11	1	10

Three patients had a double uterus. Curettings of five patients revealed cervical and endometrial polyps. Contrary to expectation, lacerated cervixes and amputations were of minor importance in the secondary group, which is in agreement with the findings of Finn regarding the influence of cervical operations on subsequent childbearing.

TABLE IX. GYNECOLOGICAL COMPLICATIONS AND TYPE OF TREATMENT IN PATIENTS WITH HABITUAL ABORTION

COMPLICATIONS	NUMBER OF PATIENTS		TREATMENT	NUMBER OF PATIENTS	
	PRIMARY (123)	SECONDARY (88)		PRIMARY (123)	SECONDARY (88)
<i>Uterus:</i>					
Retroversion uteri	50	30	Pessary	11	0
			Suspension	10	3
Myoma uteri	11	7	Myomectomy	3	2
Double uterus	2	1	None		
Cervical laceration	—	2	Repair	—	1
amputation	—	1			
Descensus uteri	—	2	None		
Polyps, cervical	3	—	Polypectomy	3	—
endometrial	1	—	Curettage	1	—
<i>Ovary:</i>					
Ovarian cyst	3	2	Oophorocyst- ectomy	1	1
			Cyst resection	2	1
<i>Salpinx:</i>					
Salpingitis	3	—	Salpingectomy	3	—
Ectopic pregnancy	1	1	Salpingectomy	1	1
Total number	74	46		34	8
Total incidence	60 per cent	52 per cent		28 per cent	9 per cent

Summary of Treatment.—The obstetric outcome of 280 pregnancies in 107 primary habitual abortion patients, and of 209 pregnancies in 88 secondary abortion patients is shown in Tables X and XI. The various types of treatment employed can be divided approximately as follows:

Type I. No Treatment. This control group of patients have been presented in Tables IV and V. They received essentially no therapy since they had aborted, were threatening to abort, or did so immediately after consulting a physician.

Type II. Empirical Treatment. This designates former therapy which was based on practical observations and accepted procedure without specific study of individual patient requirements. It includes prenatal care, complete or partial bed rest, restriction of coitus at the time of the expected menstrual period, sedation, vitamin E, progesterone, thyroid extract, and antisyphilitic therapy.

Type III. Rational Treatment. This implies specific detection and correction of certain factors, defects, and deficiencies, and represents the current treatment. It consists of antenatal care; diets high in citrus fruits, fresh vegetables, and minerals, dietary supplements including vitamin C (50 to 100 mg., three times a day), K (5 mg. daily) and minerals; complete restriction of coitus; psychotherapy; avoidance of mineral oil (which absorbs the fat-soluble vitamins); and thyroid extract when the basal metabolism rate is low. Bed rest and sedation are reserved for those with threatened abortion. Some patients also received vitamin E and progesterone, but these agents are no longer employed.

The obstetric outcome according to the various types of treatment described above has been summarized in Tables X and XI. Type III therapy gave the best results as shown by an abortion rate of only 14 per cent as contrasted with 65 per cent in the control group without treatment. It provided a corresponding increase in the full-term salvage, which was 26 per cent in the control patients and 80 per cent after Type III treatment. Current therapy also gave

Nervous tension and anxiety may result in nausea and vomiting as shown in Table XIV. Such loss of food substances can reduce the value of a normal diet and exert a greater effect on those with a poor nutrition. Dietary deficiencies were corrected, and vitamin and mineral supplements were provided. Perhaps in some patients such treatment also served as a placebo. Continuation of activity was insisted upon in order to keep the patient occupied, while bed rest was reserved for those with threatened abortion. There is no actual proof that constant bed rest is essential for a successful confinement since most women have a satisfactory termination without it.

TABLE XIV. TYPE OF DELIVERY (PREMATURE AND FULL TERM), CONGENITAL ANOMALIES, MATERNAL AND INFANTILE MORTALITY IN HABITUAL ABORTION

DELIVERY	PRIMARY ABORTION		SECONDARY ABORTION		CLINIC INCIDENCE (PER CENT)
	NO.	PER CENT	NO.	PER CENT	
Spontaneous	95	67.9	96	88.0	85
Operative:					15
Forceps	27	19.0	5	5.0	
Caesarean section	15	10.6	1	1.0	
Breech extraction	5	3.5	5	5.0	
Version	0		1	1.0	
Total number	142		108		
Congenital anomalies	3	2.0	1	1.0	2.9
Maternal mortality	2	1.4	1	1.0	0.2
Infantile mortality	5	3.5	13	12.0	3.0

At first it seemed wrong to advise these patients to conceive again and again. However, this point of view was confirmed by the actual results. A spirit of rivalry and improvement of morale replaced their previous downheartedness as they observed one another continuing successfully to term. The nursing and social services rendered valuable assistance to many patients. Some were advised to seek spiritual comfort at prayer and from the church. While psychotherapy is a necessary part of the treatment, it is most difficult to evaluate its importance statistically.

Type of Delivery and Congenital Anomalies

When a patient reaches full term after many recurrent abortions, the initial joy is replaced by apprehension of labor. Under such circumstances, analgesia is indicated and spontaneous delivery is anticipated, as shown in Table XIV. Cesarean section had a higher incidence in the primary group.

Congenital anomalies had a lower incidence in each group of patients than ordinarily occurs in the clinic population. Malpas reported a rate of 2.9 per cent, which is also extremely low. Accordingly, there appears to be no basis for stating that these patients should avoid future pregnancies.

Maternal and Infantile Mortality

Two maternal deaths followed cesarean section and one occurred after a midforceps delivery as shown in Table XIV. The infantile mortality rate in the primary group was the same as that for the clinic, but it was four times greater in the secondary abortion patients. This demonstrates the need for an increased interest and effort in the management of this type of patient even though she has a better prognosis as to full-term expectancy.

Discussion

This study had a fourfold purpose, namely, to define habitual abortion, to determine the incidence, to detect the contributing factors, defects, and de-

TABLE XII. PRIMARY HABITUAL ABORTION. SUMMARY OF CONDITIONS FOUND IN 33 PATIENTS BEFORE RECEIVING TYPE III THERAPY

CONDITION	NUMBER	PER CENT
Nutrition inadequate	27	82
Nausea and vomiting	23	70
Bed rest and sedation	30	90
Coitus in pregnancy	28	85
Psychomatic instability	28	85
Mineral oil used	15	45
Gynecological complications	19	57
Dietary deficiencies: vitamin C	17	51
prothrombin (K)	14	42
Hormone deficiency: minus basal metabolism rate	17	51
Medical complications: hemorrhagic diathesis	22	66
underweight, overweight	8	24
anemia, positive serology	6	18
Total	254, or average of 7.7 per patient	

TABLE XIII. PRIMARY HABITUAL ABORTION. SUMMARY OF TYPE III THERAPY EMPLOYED IN 41 PREGNANCIES

TREATMENT	NUMBER	PER CENT
Nutritional instructions	41	100
Nausea and vomiting control	25	61
Bed rest and sedation omitted	37	90
Coitus prohibited	41	100
Psychomatic therapy	41	100
Mineral oil prohibited	41	100
Gynecologic complications corrected	17	41
Dietary supplements: vitamin C	38	92
vitamin K	30	73
vitamin E*	28	68
minerals	18	43
Hormone supplements: progesterone	21	51
thyroid extract	17	41
Medical complications treated	14	34

It would appear that vitamin C gave slightly better results than did vitamin K, though more data are needed to arrive at any definite conclusions. However, in a separate series of patients with threatened and spontaneous abortion, vitamin C deficiency was found in nearly three-fourths of the patients.

Gradually, after omitting various agents and methods from the therapy, one may ultimately discover which procedure is responsible for the favorable results and thereby ascertain the pathogenesis of habitual abortion. At the present time, one must conclude that there are several causative factors and several remedial agents and procedures. Among the latter are vitamin C, sexual abstinence, and psychotherapy.

Psychosomatic Obstetrics

Perhaps nowhere in the field of medicine does one encounter as many emotionally unstable patients as in cases where there is no offspring. The docility and equanimity of the usual obstetric patient are lacking. The habitual abortion patients are apprehensive, fearful, and cry easily. Physicians have endeavored to console them by stating that nature has deliberately cast off an abnormal child. This serves to increase a guilt complex that is invariably present. They always ask: "Why do I abort?" Sometimes they add: "My husband says it is my fault." In days gone by, the Puritans interpreted miscarriage as signifying intercourse on a holy day. It would be interesting to know their reasons for this point of view.

abortions. Vitamin E and progesterone were introduced and great reliance was placed on these agents. Not infrequently, the habitual abortion patients were referred to the Sterility Clinic for appraisal of their problem, even though none of them exhibited any particular difficulty in becoming pregnant.

A Special Clinic was established in 1940 for the study and treatment of habitual abortion. Patients made regular antenatal visits and various tests and determinations were obtained, as tabulated in Tables XII and XIII. Meanwhile, vitamin K had engaged the interest of obstetricians with regard to hemorrhagic disease of the newborn. Together with vitamin C, it became the subject of an investigation reported by Javert and Stander. This focused attention on the importance of the nutritional aspects of habitual abortion and certain dietary supplements were administered according to individual patient requirement. The Warner, Brinkhous, and Smith test was used for the plasma prothrombin determinations and at first many low values were obtained and reported. This test, as modified by Summerson and Bonsnes, now reveals normal prothrombin values in habitual abortion. This led to the discontinuance of vitamin K therapy in ten patients who had a satisfactory outcome. However, because of insufficient data, this vitamin is still employed in our present regimen. By a gradual elimination of all agents and methods, one may ultimately discover the pathogenesis of habitual abortion. Unfortunately, certain circumstances required that the Special Clinic be discontinued in September, 1947, so that clinical management of these patients has reverted to the use of Type III therapy on an empirical basis with a continuation of the good results.

Conclusions

1. A patient having three or more consecutive spontaneous abortions beginning with the first pregnancy is regarded as having "primary habitual abortion."

2. A patient is designated as having "secondary habitual abortion" when three or more consecutive abortions follow delivery of one or more immature, premature, or full-term infants.

3. An abortion is rigidly defined as a pregnancy ending at 22 weeks' gestation or less and resulting in a fetus weighing 500 Gm. or less.

4. The incidence of primary habitual abortion is 1:300 and for the secondary variety it is 1:493.

5. One hundred twenty-three primary habitual abortion patients had 669 pregnancies, and 88 secondary abortion patients had 679 pregnancies, making 1,348 in all for analysis.

6. The uncorrected abortion rate without treatment was 65 per cent for the primary group, and 46 per cent for the secondary group of patients with a corresponding full-term expectancy of 26 per cent and 47 per cent, respectively, showing a somewhat better prognosis for the secondary habitual abortion patient. This was offset in part by an infantile mortality rate of 12 per cent for these patients.

7. The histories, physical examinations, and laboratory determinations of both the primary and secondary groups revealed the same multiple factors, defects, and deficiencies.

iciencies, and to evaluate the results obtained by the correction of these conditions. The histories, physical examination, and laboratory determinations revealed multiple conditions which were essentially the same in both groups of primary or secondary habitual abortion patients. These patients were rigidly classified even though it means losing a good many who had fetuses just over 500 Gm. Multiple therapeutic agents or methods were employed with gratifying results as shown by the reduction of the abortion rate from 65 per cent to 14 per cent, with a corresponding increase in the full-term salvage from 26 per cent to 80 per cent. However, it is equally important to mention five primary abortion patients who had 7, 8, 9, 10, and 12 consecutive abortions, respectively, and never succeeded in reaching viability. Several of these have since adopted children.

Unfortunately, it is difficult to assess the individual merit of any single agent or method. Gradually, certain items such as vitamin E and progesterone were eliminated without noticeable impairment of the end results. Similarly, vitamin K has been omitted from the treatment given to ten patients who went to term. While these agents corrected an underlying deficiency, they may have had also a placebo effect. Therefore, it is equally difficult to evaluate the benefits of psychotherapy.

Some light may have fallen on the pathogenesis of habitual abortion. Lack of antihemorrhagic vitamin C and possible K may precipitate decidual bleeding leading to premature separation of the placenta and ultimate spontaneous abortion. Certain patients showed evidence of hemorrhagic diathesis as manifested by nasal, gingival, rectal, and dermal bleeding in addition to vaginal bleeding of threatened abortion. Many of these patients had low values for ascorbic acid in blood plasma and others were also low in prothrombin concentration. Moore et al. have concluded that vitamin K deficiency was a factor in producing abortion in rabbits.

There is such a maze of literature that proper cognizance cannot be taken of all of the pertinent articles. As the reader reviews them in order to develop his own philosophy, let him be reminded of three important matters: the high percentage of success irrespective of which vitamin, hormone, or method is employed; the lack of specific information as to the pathogenesis of human spontaneous abortion.

It is of interest to review the treatment of habitual abortion at the Woman's Clinic since its establishment in September, 1932. At that time, it was the usual practice to employ empirical treatment based on clinical experience and observation. Complete bed rest was insisted upon, and intercourse was permitted or interdicted only at the time of the expected menstrual period. Thyroid extract was in vogue, and antisyphilitic therapy was occasionally recommended on the history of recurrent abortion. The advent of the Wassermann test put a stop to indiscriminate antisyphilitic therapy. Little or no attention was paid to diet, nutrition, and anemia.

The first patient to receive nutritional consideration of habitual abortion was placed on a high-vitamin, high-iron diet by one of us (C.T.J.) in 1936. This patient was delivered of a full-term child after having sustained three previous

PERITONEAL BODIES AND CYSTS OF THE BROAD LIGAMENT*†

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A LENGTHY, detailed, and highly intuitive paper by Walthard, published in 1903, was concerned with epithelial inclusions in the ovary. The majority of his data had to do with germinal epithelium inclusions. In addition, he described two ovaries which contained small solid epithelial bodies, noted that similar structures were found in and under the serosa of the tube, and commented that they may undergo cystic changes in this location.

Nowadays the original subject of Walthard's study has been forgotten but these solid and cystic epithelial structures have been termed Walthard's bodies in many publications, whether they are found in the tube or in the ovary.

The name "Walthard bodies" is inappropriate. In the first place, Walthard was a latecomer in describing them. Second, and of more importance, the use of a man's name for an anatomic or pathologic structure is an objectionable and confusing practice. Terminology should have descriptive or etiological significance. The use of a man's name, no matter how respected, leads to confusion. Consequently, in the material to follow, these structures will be referred to as peritoneal bodies or epithelial knots, and their cystic derivatives as peritoneal cysts.

As previously stated, Walthard was not the first to describe these structures. In 1902, Schiebele devoted many pages to this subject, citing ten authors who had previously described or discussed them. In 1903, Robert Meyer mentioned articles devoted to or referring to them by six additional authors. Werth, in 1887, gave the first adequate description and discussion of this subject, according to Meyer. Plant in 1933 also credits Werth with the first good description of these bodies.

Recently (1946) Reis has discussed these "cell balls" and their cystic derivatives. More recently Moore (1947) considered these structures and their cystic derivatives so rare that he published a report on the findings in one patient. He stated that a total of only 266 cases had been reported in the literature. We have made no attempt to check the accuracy of this claim.

Material

The material was derived from routine slides of one or both salpingo-oophorectomy specimens from 150 patients. In addition, the lateral half of the tube, broad ligament and ovary from 16 patients has been serially sectioned and studied. Routine sections were stained with hematoxylin and eosin; in

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8. Current therapy is based on the detection and correction of all contributory conditions and consists of dietary instructions, dietary supplements such as vitamins C and K and minerals, abstinence from intercourse, continued ambulation and activity, psychotherapy, thyroid extract as indicated, elimination of gynecologic disease, and avoidance of mineral oil.

9. The above regimen yielded a full-term salvage of 80 per cent in the primary group and 100 per cent in the secondary group with a corresponding reduction in the primary abortion rate to 14 per cent.

10. It is impossible to state which vitamin, hormone, or method was responsible for the good results. Elimination of vitamins E, K, and progesterone from the regimen did not seem to impair the outcome.

11. Vitamin C deficiency may predispose to the production of decidual bleeding (threatened abortion) and to premature separation of the placenta and ultimate spontaneous abortion.

12. Coitus in pregnancy may precipitate abortion in predisposed patients.

13. Threatened abortion (premature separation) and placenta previa had an increased incidence in the habitual abortion patients.

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Location.—The impression is current that these structures are found only on or just beneath the serosa of the tube. A group of 67 solid or cystic bodies in which the position could be accurately determined was tabulated; 33 were on the tube and 34 on other areas of the broad ligament. In this latter location, nine were on the mesovarium and the remainder (25) on the mesosalpinx.



Fig. 2.—Small cystic body under surface of mesovarium. Note the uniform darker staining cytoplasm and early pyknotic changes in nuclei of cells lining cavity.

It should be noted that most routine blocks were cut to include tube, mesosalpinx, mesovarium and at least part of the ovary. It was thus possible to survey the serosal surface of all the constituents of the broad ligaments in a single section. (In most laboratories, blocks of the tube and ovary are cut separately and the broad ligament is not included. We believe that this is the likely explanation for the current misconception regarding the usual position of these structures.)

Position in Relation to Surface.—The probable mode of development of these structures from peritoneal mesothelium will be discussed later. However, consistent with this histogenesis, a few of the solid bodies showed direct continuity with the mesothelium (Fig. 5). Only a portion of the epithelial mass was therefore subserosal. In other routine specimens, solid bodies and some showing a moderate degree of cystic dilatation were located immediately under but not continuous with the mesothelium. Possibly some of the other solid bodies found in routine sections would have shown continuity with the mesothelium had serial sections been made. In several of the serially sectioned specimens such continuity could be demonstrated. On the other hand, several were observed in the serials that were just subserosal, but there was no continuity with the mesothelium. Still other solid bodies were noted to be separated from the serosal surface by a definite layer of connective tissues (Fig. 6). This

addition, Milligan trichrome and iron hematoxylin with mucicarmines have been used.

Findings.—These solid or cystic structures have been noted in specimens from 78 patients. A total of 58 solid bodies and 78 of their cystic derivatives have been found. These data do not include the findings in two serially sectioned specimens. One surface of one broad ligament and both surfaces of the other were literally covered by these solid or cystic structures. The exact number has not been counted. In the routine tissues the number of solid bodies varied from one to three per specimen. The number of cystic structures varied from one to twelve.

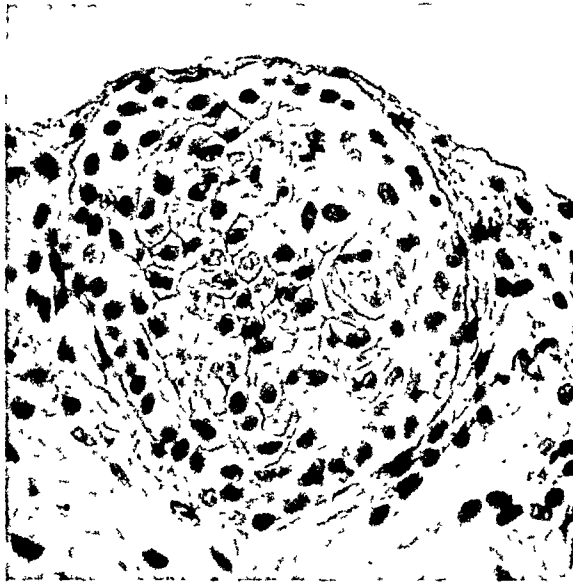


Fig. 1.—Solid epithelial body just under intact serosa of mesosalpinx. Note distinct cell membranes.

Morphology.—The solid bodies (Fig. 1) are composed of a mass of epithelial cells which possess distinct cell membranes, faintly staining cytoplasm, and vesicular nuclei with little or no chromatin. As described by Varangot (1938) and D. N. Danforth (1942), there is an infolding of the nuclear membrane. Under oil immersion this infolding frequently gives the nuclei bizarre shapes. There are no intercellular bridges and no basement membrane surrounds the body. There is no true capsule although compression of adjacent connective tissue may give the false impression of a capsule.

The word "squamous" has frequently been used in reference to this epithelium. As pointed out by Ralph Reis, it is not squamous epithelium. There is no flattening of the epithelium either in the solid bodies or in the larger bodies with small cavities. Flattening occurs only when cystic dilatation is fairly extensive.

The process of cavity formation and cystic dilatation can be observed in various specimens. Occasionally, in early cavity formation the immediately adjacent epithelial cells are cuboidal and rarely even columnar (Fig. 2). This appearance, we believe, must be interpreted as a degenerative phenomenon since the nuclei are frequently pyknotic and the cytoplasm of such cells takes on a uniform glassy but deeper stain.

With the accumulation of further fluid, the number of layers of cells in the wall becomes less and the degree of flattening of the cells in the luminal layers becomes greater (Figs. 3 and 4). In the larger cysts the epithelium consists usually of two layers of flattened cells; more rarely, of only a single layer.

Differentiation From Cysts of Mesonephric or Paramesonephric Origin.—We have recently presented the detailed histologic characteristics of cysts of the broad ligament derived from the mesonephric duct, mesonephric tubules, and aberrant paramesonephric (tubal or Müllerian) epithelium (Gardner, Greene, and Peckham 1948). In adequate tissue preparations they can be differentiated with certainty from peritoneal bodies and peritoneal cysts. Cysts of mesonephric or paramesonephric origin have a true capsule in which muscular elements can be identified with a Milligan trichrome stain; peritoneal cysts do not have a true capsule. The epithelium of cysts of mesonephric duct origin is single-layered, cuboidal, and has a basement membrane. That of mesonephric tubule origin is more columnar and is composed of two types of cells, lightly staining ciliated cells and more darkly staining nonciliated cells. The epithelium of cysts of paramesonephric origin is identical to that of the oviduct or tube and is composed also of two types of cells, ciliated and secretory. The epithelium of peritoneal cysts on the other hand is composed of flattened cells, usually two layers in thickness.



Fig. 5.

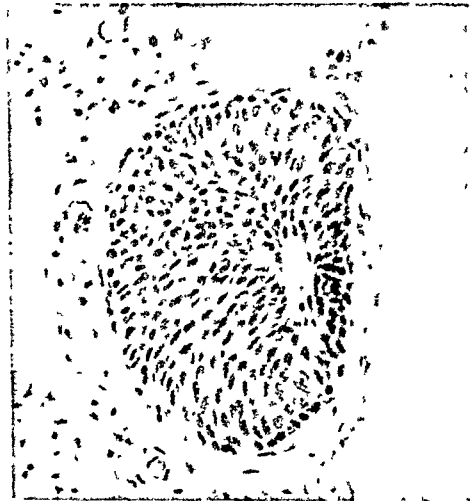


Fig. 6.

Fig. 5.—Two small bodies on surface of uterine tube. One is continuous with peritoneal mesothelium; the other is immediately subserosal.

Fig. 6.—Small epithelial body with minute cavity. It is separated from serosa of mesosalpinx by thin layer of connective tissue.

Histogenesis.—Four main theories have been proposed to explain the histogenesis of peritoneal bodies, the so-called Walthard bodies:

One of the earliest was that these bodies represent or are derived from accessory adrenals. According to Rossa (1898), these solid bodies are accessory adrenal tissue and cysts result from atrophy of this tissue. While accessory adrenals may be found in the broad ligament, their resemblance to these epithelial bodies is indeed slight and most superficial. At present no one holds a brief for this suggested histogenesis.

The second main theory was proposed by Schickele (1902). He believed that they developed *in situ* from surface epithelium. This surface epithelium, however, was not ordinary peritoneal mesothelium but ovarian germinal epithelium which had migrated to this aberrant location in an unknown manner due to an unknown stimulus. The belief that these bodies develop from ovarian germinal epithelium rather than peritoneum seems unnecessarily complicated.

was also true of bodies that showed more than a moderate amount of cystic dilatation. A few of the moderate-sized cysts were entirely below the serosal surface; the majority, however, bulged above the surface level (Figs. 3 & 4). Some were truly sessile or even semipedunculated; this was usually true of the larger cysts.

In a few of the routine sections solid and cystic bodies were apparently deep in the substance of the broad ligament. However, extensive adhesions were present in each instance due either to a previous pelvic inflammatory process or to endometriosis. Consequently, we believe that this location was an artifact, due to distortion of tissues by the coexisting adhesions. Serial sections would probably have demonstrated their near proximity to peritoneal clefts or infoldings. This opinion is neither unique or original. It was expressed by Robert Meyer in 1903.

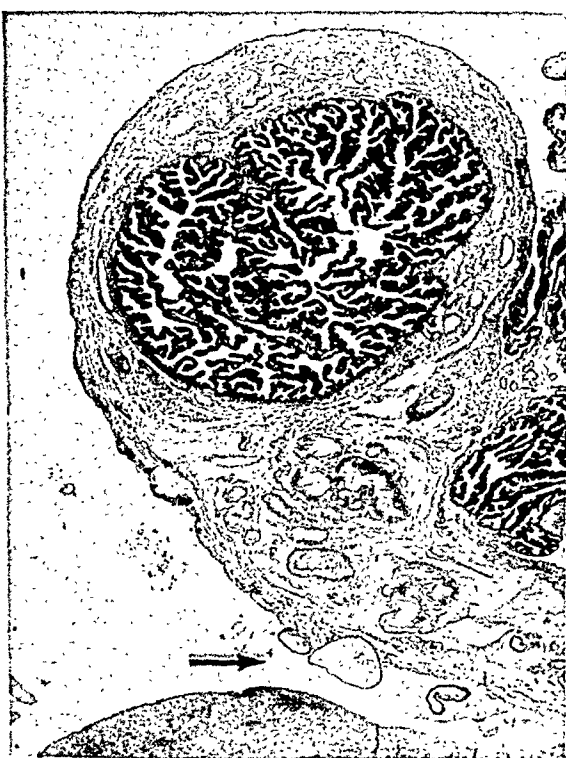


Fig. 3.



Fig. 4.

Fig. 3.—Low power photomicrograph with arrow pointing to two cystic bodies on surface of mesosalpinx.

Fig. 4.—High power of Fig. 3 showing sessile position of most of the larger cystic body.

Inflammatory Reaction.—Gross pathology reports and microscopic specimens from 35 patients were studied in particular for evidences of present or past inflammatory reactions; it was found in 32 specimens. The microscopic evidence of active inflammatory reaction was quite obvious; it was usually a subacute perisalpingitis associated either with ectopic pregnancies or more frequently with endometriosis. Adhesions alone or in association with other old inflammatory residuals were found in the others. These, too, were associated either with residues of pelvic inflammatory disease or with endometriosis. In the remaining three specimens there was no evidence of present or past inflammatory reaction. It is possible, of course, that such inflammation had occurred in the past but had left no permanent residuals.

the other hand, we found two definite solid epithelial bodies in serial sections (Fig. 7). These were identical in all details with those of the tube and broad ligament. In one specimen direct continuity could be demonstrated with an area of piled up germinal epithelium. The other was directly under the germinal epithelium but separated from it by a thin layer of ovarian stroma. A third specimen in the cortex of an ovary had several solid cords of similar epithelial cells imbedded in a fibrous stroma. This is not included, however, since we are uncertain whether it is, or is not, a true, but minute, "Brenner tumor."



Fig. 7.—Solid epithelial body in cortex of ovary. This specimen showed no continuity with the surface epithelium.

Conclusions

Solid epithelial bodies and their cystic derivatives are found relatively frequently under the serosa of the tube and the broad ligament. The commonly used name "Walthard bodies" is considered inappropriate because personalized nomenclature is confusing and, in regard to priority, Walthard was actually a latecomer in describing these structures.

The solid and cystic structures are found with no greater frequency under the tubal serosa than under the remaining surface of the broad ligament. They are extremely rare in the ovary.

They arise from the peritoneal mesothelium in response to and as part of an inflammatory reaction.

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A third theory of histogenesis was added fairly recently by Ralph Reis. He suggested that they developed from misplaced entodermal cells of cloacal origin. His reason for this suggestion was the close similarity of these structures to cell balls of Limbeck and Brunn which are found under the vesical and ureteral mucosa.

This theory seems unlikely. The fact that two structures are morphologically similar does not prove that they have the same embryonic derivation. In fact, while the bladder is largely derived from cloacal entoderm, the ureter where similar cell balls are found is derived from the mesonephric duct—a mesodermal derivative.

A fourth and commonly accepted histogenesis was proposed and well demonstrated by Werth in 1887. He showed that these bodies develop as proliferations of the peritoneal epithelium. He was able to demonstrate continuity in some instances between the epithelial bodies and the overlying serosal epithelium. Various subsequent workers have accepted this mode of development and have also been able to demonstrate similar continuity. In 1903, Robert Meyer published a thorough and most convincing study on this subject. He showed the early stages of proliferation of the peritoneal epithelium and subsequent development of these solid and cystic bodies. His report was based on the findings in solid and cystic structures from 16 specimens. In each case there was evidence of present or past inflammatory reactions. Consequently, he concluded that these bodies occur as a response by the peritoneum to inflammatory processes.

Our findings, particularly in serial sections, are similar to those first described by Werth in 1887, and fully amplified by Meyer. Various stages in the development of these structures have been noted from the early localized areas of proliferation of the mesothelium, the downgrowth of epithelial masses, sub-serosal masses of epithelial cells no longer connected to the mesothelium, early cystic degenerative changes in the center of these masses and the final end result, peritoneal cysts.

We could find no evidence of present or past inflammatory reaction in three of our specimens. It is possible, however, that these tissues had, in the past, been subjected to a mild inflammatory reaction which had, however, left no permanent residues. It must be remembered that bacterial inflammation is not the only factor that may lead to the development of these structures. That chemical irritation from blood is sufficient to cause their production is evinced by their frequency and easily observed early stages of development, not only with tubal-pregnancy specimens but also in cases of endometriosis. It is even conceivable that they may arise as the result of chemical irritation from a small amount of intraperitoneal bleeding associated with rupture of a follicle. If this were the case, one would not expect to find permanent residues of an inflammatory reaction.

“Walthard Bodies” in the Ovary.—As previously stated, Walthard's original paper was concerned with germinal epithelial inclusions in the ovary. In fact, the solid epithelial bodies given his name constituted only a minor part of his paper. Furthermore, solid epithelial bodies in the ovary similar to those found under the serosa of the tube and broad ligament are very rare in our experience.

In a deliberate study of sections from 100 ovaries, D. N. Danforth found only one solid body of this type, although he found four other cystic derivatives. On the other hand, he found 13 solid and 43 cystic bodies on the tube and mesosalpinx in 350 routine sections.

We found none of these solid bodies and no structures which we could identify as their cystic derivatives in the ovaries of our routine sections. On

Finally, I consider the effort to eliminate proper names from anatomical nomenclature to be important and commendable. However, one might object to the suggested term "peritoneal bodies" on the grounds of their admitted occurrence in the ovary, an organ which, strictly speaking, has no peritoneal covering.

DR. RALPH A. REIS.—The essayists report the frequent finding of cell balls or nests in the subserosa of the uterine tube and of the broad ligaments. They emphasize the fact that these cell balls are not made up of squamous epithelium and that they are not the so-called Walthard bodies. With both of these conclusions we are in full accord. Anyone who has studied these cell balls must agree that they are made up of transitional cells.

A study of Walthard's original article will show that he reported on cell rests in the ovary in which the individual cells were made up of nonvesicular nuclei, deep pyknotic cytoplasm, no distinct cell membrane, and were coffee bean shaped as recently emphasized by Danforth. Last, the cell masses are embedded in a network of trabeculated connective tissue. Brenner tumor cells are similar and are likewise embedded in a connective tissue stroma. These differences have been previously emphasized in the discussion of our report of 1946.

A consideration of the etiology of these cell masses raises many interesting questions. The essayists report evidence of inflammation in some 32 and no such evidence in only three specimens. In these latter, they presuppose pre-existing inflammation even though no evidence of such can be found. This conclusion is open to serious question. All the uterine tubes under consideration were removed for cause; therefore inflammation and pathology were found in practically all. In our series, only normal tubes were studied and all tubes showing any evidence of inflammation were carefully excluded. Yet in our study, six out of ten, when studied by serial section, showed these selfsame cell balls. Certainly, then, it would seem that pre-existing inflammation is not necessary and that no one has the right to assume that inflammation must have been present to account for these cell balls.

Furthermore, our studies showed that with the formation of cysts within these cell balls, the transitional cells forming the innermost lining of the cysts assume first low cuboidal, and later high cuboidal shapes while the cells situated peripherally remain transitional in character. We do not agree with the thought that the cells lining the cysts are undergoing a degenerative process.

We are still of the opinion that the change, as first described by Saphir and Kurland, from transitional cells to cuboidal cells, is a reversion to an embryologically younger form of epithelium. It is an excellent example of "dedifferentiation." It has been repeatedly stated that new cells, under the influence of irritation, regeneration, or tumor growth, will undergo a dedifferentiation or reversionary process in the direction of the primary embryonal or blastomere cell. With further growth there is a redifferentiation to form a cell not identical with the original type. This new differentiation results in cells of a lower order of specialization than the original. This is progressive or prosoplastic metaplasia.

Limbeck and Brunn reported similar cell balls with similar cyst formations in the wall of the bladder, the ureter, and the kidney pelvis. Saphir and Kurland found the same structures and were able to trace the development of adenocarcinomas of the bladder to such cell balls. It is, of course, hazardous to conclude similarity of origin from the fact that structures closely resemble each other morphologically. Histologically, cell balls of the urinary tract and of the tube seem similar, and undergo cystic changes in a similar manner.

The clinical significance of these cell balls of the tubal wall lies in the possibility that they may undergo malignant changes as do those of the urinary tract. This question cannot be answered at this time. However, may I recall to you, that we have recorded a primary papillary transitional-cell carcinoma of the uterine tube which probably took its origin from such epithelial cell balls. A second carcinoma was also recorded which consisted of both transitional epithelium and glandular structures. It is possible that this second tumor also arose from such cell balls of the tubal wall.

Finally, the essayists have again emphasized that "terminology should have only descriptive or etiological significance." May I respectfully call their attention to the repeated use of the term "Milligan stain"?

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Discussion

DR. D. N. DANFORTH.—Although there are certain points with which one might differ, this paper is nevertheless one of the major contributions to our knowledge of these minute but fascinating cell masses. Most important, this work shows by the serial section technique the lengths to which they may extend, and their variations. Further, when considered with other work by the same authors, it clarifies the distinction between the cystic nests and the mesonephric and paramesonephric derivatives, which to most of us have been so very confusing.

My own experience with these cellular accumulations is limited for the most part to a study of single routine microscopic sections of 350 normal tubes. Among this material, 56 sections contained cell nests. Thirteen, or 23 per cent, were solid, and the remainder showed cystic change. In this study, my interest was directed almost entirely to the curiously grooved nuclei which are a constant and striking feature of the solid cell masses, and occur with less frequency in the cystic ones. Although similarly marked nuclei occur in many other situations, I have never before or since seen them in such profusion and constancy except in the Brenner tumor of the ovary, of which this nucleus is also a characteristic feature. The chief difference between the material presented tonight and that to which I have just referred is that in one inflammatory changes were a prominent feature, whereas in the other the tissues were normal. In both, the cell bodies are morphologically similar.

The most important conclusion which the essayists make is that the cell masses are inflammatory in origin. The evidence which they present in favor of this thesis is the finding of associated inflammatory conditions in 32 out of 35 cases. In normal tubes, identical rests are considered as a remote effect of inflammation, the inflammatory process having healed, or been subclinical, or subpathological. There is no evidence that in the infected material the nests did not originate before the onset of the associated inflammatory disease for which the adnexa were evidently removed. Also, if the solid nests and plaques, which in our material abound with grooved nuclei, are the form in which these structures originate, it is difficult to relate the appearance of such distinctive tissue to inflammation, either chemical or bacterial, as we know it elsewhere in the body. In fact, all of the classical signs of inflammation are lacking. The serosa of the tube, from which the bodies are said to arise, is similar to the peritoneum which is found throughout the abdomen. If these structures occur in response to inflammation, and especially since they are often visible grossly, would they not be found in abundance elsewhere on the peritoneum, as over the appendix, or gall bladder, or uterus? And would there not be a lingering lymphocyte or polymorphonuclear leucocyte? Further, if, as Meyer and others have postulated, these nests as seen in the ovary are related to Brenner tumors, are these tumors also considered as a response to inflammation? If this were the case, the Brenner tumor would parallel tuboovarian disease in frequency, rather than maintain its place among the rare ovarian tumors.

I have had no occasion to study neonatal or pediatric autopsy material except for the examination of casual specimens. In one of these, a healthy nest, complete with grooved nuclei, was found in the mesosalpinx on routine examination of the adnexa of a 4½-month-old infant. The cause of death in this infant was congenital heart disease, with coarctation of the aorta, cardiac hypertrophy, and pulmonary edema. There was no history or finding of inflammation about the adnexa. For these reasons, although it is possible that associated inflammation may stimulate the proliferation of these structures, I believe that their origin remains obscure.

THE SELECTIVE MANAGEMENT OF PLACENTA PREVIA*

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PLACENTA previa continues to be one of the more serious complications of pregnancy. Davis and Campbell have estimated that 15 to 20 per cent of the maternal deaths in the country at large are the result of placenta previa, either from severe hemorrhage or from subsequent embolism or infection. There has been some controversy regarding the management of this complication. One group believes that the treatment resolves itself simply into either rupture of the membranes or cesarean section. The other group continues to use the Voorhees bag, the Willett forceps, version, and other methods in treating this condition. This paper is concerned with an analysis of the incidence, treatment, and results obtained in the cases encountered at the Mayo Clinic from 1919 through 1945.

Incidence

The incidence of placenta previa has been reported as ranging from 0.32 to 2 per cent. In the period covered by this study, Jan. 1, 1919, through Dec. 31, 1945, there were approximately 12,000 deliveries on the service of the Department of Obstetrics and Gynecology of the Mayo Clinic in the hospitals of Rochester, Minn. Placenta previa complicated these deliveries 134 times, an incidence of 1.12 per cent, or 1 in 89 deliveries. These 134 cases represent 129 mothers, as 5 patients had one repetition of placenta previa. This incidence of recurrence of this complication is high. Aaberg stated that recurrent placenta previa is an uncommon obstetric complication. He found only two cases of repetition at the Boston Lying-in Hospital from 1925 to 1946. Persall and Torpin also stated that placenta previa seldom occurs in the same patient twice.

Placenta previa has been consistently reported as occurring more frequently in multiparas than in primiparas. In our series 26, or 19 per cent, were in primiparas, and 108, or 81 per cent, were in multiparas. Why multiparas are more subject to this condition is unknown.

Malpresentation is quite common in placenta previa. In our series the incidence was 12 per cent, of which 7.5 per cent represented breech presentations, and 4.5 per cent transverse position. This high incidence was probably the result of the space occupied by the lowlying placenta. Twin pregnancy occurred in 5 per cent, or once in every 19 cases, as compared with a normal of once in 87 pregnancies. A high incidence of placenta previa in twin pregnancy has been noted by other authors,²² due probably to the fact that the increased surface area of the placenta or placentas increases the chances of low implantation.

We have classified placenta previa into five types: lowlying, lateral, partial, central, and the rare cervical type. This classification⁸ is described in detail by Greenhill. The incidence of each type in our series is given in Table I and needs no discussion.

Treatment

General Treatment.—Individualization in each case has been the underlying principle of the management of placenta previa at the clinic. However,

*Read at the meeting of the Minnesota Obstetrical and Gynecological Society, Rochester, Minn., May 1, 1948.

DR. GREENE (Closing).—Dr. Danforth and I have discussed and disagreed on these subjects before. I cannot help but feel that he is overemphasizing the significance of the coffee bean or infolded nucleus. It is found in the so-called "Walthard body" and in the Brenner tumor, but it is also found in many other structures and locations in the body. Such nuclei are common in the germinal epithelium, stromal cells of the ovary, rete epithelium, and medullary cords and tubules of the ovary. They are frequent in the peritoneal mesothelium covering the appendix, the broad ligament, and even in the serosal surface of the uterus. I have seen them in urethral and bladder epithelium, in the cervix in areas of epidermidization and even in a poorly differentiated squamous-cell carcinoma of the cervix where they appeared in profusion.

Concerning the importance of inflammation in the etiology of the peritoneal bodies, we again disagree. In Dr. Danforth's original report on "Walthard bodies," he examined only normal tubes and ovaries. No doubt the endosalpingeal portions of the tubes were normal. However, some of his patients were operated upon for endometriosis. With this latter condition, a mild to moderate perisalpingitis with infiltration with plasma cells and lymphocytes was extremely common in our preparations.

In regard to Dr. Reis' discussion: We stand justifiably rebuked for our own misdemeanor in using "personalized" terminology. He also disagrees as to the etiological importance of inflammation. Perhaps none of us are quite agreed on exactly what are the evidences of past inflammation.

We do not feel too lonesome in our stubbornness in this regard. We have good company. In fact our observations are not original but merely agree to what has previously been reported by Robert Meyer and many others.

visualized satisfactorily. In these patients the placentogram is of distinct help. When it is determined that the placenta is *not* in the zone of dilatation, the patient is examined vaginally to determine the cause of bleeding, and any indicated treatment is instituted.

When placenta previa is diagnosed by placentogram, some method of delivery is selected, as the continuation of pregnancy is often fraught with danger. Hemorrhage can be combatted, but delay only increases the hazards of infection in the presence of vaginal bleeding. In a very small number of carefully selected cases prior to viability of the fetus, vaginal examination is withheld and the patient remains in the hospital until the fetus is large enough to be delivered alive. This is usually done only in situations in which it is of more than usual importance that a living infant be obtained. A roentgenologic diagnosis of placenta previa is of particular help in the management of the condition in these occasional cases.

When the placentogram has not helped in the diagnosis, a vaginal examination is done, a second room being kept ready for section. In spite of improved roentgenologic techniques, vaginal examination remains the only conclusive method of diagnosing placenta previa. Once the obstetrician has committed himself to vaginal examination, treatment is indicated at once, as a delay of a few days markedly increases the risk of infection.

Active Management.—The plan of management in our cases is summarized in Table III. Thirty-seven patients, or 28 per cent, had minimal bleeding and required no treatment.

TABLE III. TYPE OF TREATMENT

TREATMENT, TYPE	PLACENTA PREVIA, TYPE				TOTAL	
	LOW- LYING	LATERAL	PARTIAL	CENTRAL	CASES	PER CENT
No treatment	14	3	20		37	28
Ruptured membranes	7	2	19		28	
Voorhees bag	1	2	14		17	
Version		1	6	3	10	46
Bag and version			4	1	5	
Bag and Willett forceps			1		1	
Bag and breech extraction				1	1	
Cesarean section	1*	1	11†	22	35	26

*Section performed because of hypertension.

†In 2 of the 11 cases, section was performed after use of bag failed to control bleeding.

Central placenta previa was treated by cesarean section, with five exceptions. Four of these patients, with still or previable fetuses, were treated by means of version or bag and version after perforating the placenta. The other patient with a breech presentation was treated with a bag placed extraovularly; a living child was obtained. In this case only a lip of the placenta covered the cervical os, the main portion lying in the lower uterine segment. In all five cases vaginal manipulation controlled the hemorrhage. The procedure of version and extraction should be kept in mind in treating the patient who has a central placenta previa associated with fetal death or previability, and with complete or almost complete dilatation of the cervix when the patient is first seen. Delivery may be accomplished and bleeding controlled in some of these cases more rapidly with this procedure than with section.

Abdominal delivery was used in 35, or 26 per cent, of the cases. In 22 of these cases there was a central placenta previa. Cesarean section was employed in approximately 81 per cent of the cases of complete placenta previa, and in

certain general measures are applied in all cases. Preparation for the various obstetric complications is started at the first prenatal visit. In particular, preparations for possible hemorrhage are carried out by determinations of hemoglobin, blood grouping, and Rh factor on each pregnant woman. A large central blood bank, including several bottles of group O, Rh negative blood, makes rapid treatment possible. Although there are plasma, fluids for intravenous use, acacia, and gelatin on hand at all times, whole blood is preferred in the treatment of obstetric hemorrhage.

TABLE I. DISTRIBUTION OF CASES BY TYPE OF PLACENTA PREVIA

	PLACENTA PREVIA, TYPE				
	LOWLYING	LATERAL	PARTIAL	CENTRAL	CERVICAL
Cases	23	9	75	27	0
Per cent	17	7	56	20	0

The house staff is also prepared in advance for obstetric hemorrhage. From the first day of their service the gravity of vaginal bleeding is stressed. Their alertness in getting transfusions and other treatment under way, and in obtaining help from the senior obstetric staff has had a considerable influence on the prognosis for patients with placenta previa.

Painless bleeding in the later weeks of pregnancy should be regarded as arising from placenta previa until proved otherwise. All of the patients with this symptom are hospitalized for study. It is not in the scope of this paper to discuss the differential diagnosis of bleeding in the third trimester. However, circumvallate placenta¹² should be mentioned, as bleeding from this cause may be confused with that from placenta previa; in the literature circumvallate placenta has not received the attention it merits. Table II indicates that almost 80 per cent of the patients with placenta previa show symptoms before term is reached, and 25 per cent actually show symptoms prior to viability of the fetus. Thus, in planning treatment, prematurity becomes an important factor in four cases out of five.

TABLE II. ONSET OF SYMPTOMS*

WEEKS PREGNANT	PLACENTA PREVIA, TYPE					TOTAL	
	LOWLYING	LATERAL	PARTIAL	CENTRAL		CASES	PER CENT
Less than 28	1	1	8	4		14	10
28-29	1	0	5	2		8	6
30-31	4	0	6	2		12	9
32-33	0	1	6	5		12	9
34-35	1	1	9	2		13	10
36-37	5	3	16	5		29	22
38-39	2	2	11	3		18	13
40+	9	1	14	4		28	21

*Twenty-five per cent of symptoms occurred prior to viability, 79 per cent prior to term.

If the bleeding is severe on entry of the patient into the hospital, transfusion is started and the patient is taken directly to the delivery room for vaginal examination. Rectal examinations are avoided on patients with vaginal bleeding. A second room stands ready for cesarean section. Further treatment depends on the result of the vaginal examination and on other factors which will be discussed later.

If on entry of the patient the bleeding is not severe enough to demand immediate attention, a placentogram and a cystogram usually are ordered. These roentgen examinations often give inconclusive results; such results are disregarded. There are, however, a reasonable number in which the placenta can be

the bleeding. Barrett has stated that he packs the uterus routinely with iodoform gauze after either vaginal delivery or section in cases of placenta previa. In one of our patients, hemorrhage in the third stage was severe enough to necessitate hysterectomy. This operation should always be kept in mind as a possible lifesaving procedure in severe postpartum hemorrhage.¹¹

Supportive Treatment.—The replacement of lost blood is the most important adjunct to the treatment of placenta previa. Table V summarizes the data on blood loss in our series. Over half of the patients had an estimated blood loss of less than 500 c.c. (grade 1). However, in placenta previa one cannot anticipate when minimal bleeding will suddenly become severe. It is our custom to "keep ahead" of the bleeding rather than to lag behind in the use of transfusion. Blood replacement before shock can develop is practiced. Continuous estimation of the amount of hemorrhage as it occurs is necessary as a guide to transfusion.

TABLE V. BLOOD LOSS

AMOUNT		PLACENTA PREVIA, TYPE				
GRADE	C.C.	LOWLYING	LATERAL	PARTIAL	CENTRAL	TOTAL
1	500 or less	21	4	36	12	73
2	501 to 1,000	0	3	29	8	40
3	1,001 to 1,500	2	2	8	7	19
4	1,501 or more	0	0	2	0	2

Each patient is given citrated blood of her own group and Rh factor from the hospital blood bank without awaiting cross matching. This has not resulted in an increase in transfusion reactions. However, cross matching is practiced when time permits.

If shock is present to the extent that veins are collapsed, transfusion is performed with positive pressure to hasten the replacement of lost blood. On occasion we have given the first 500 c.c. of blood in seven or eight minutes, and at times the blood is run into two separate veins simultaneously. The other usual supportive measures are employed. As soon as these measures are well under way, treatment directed at obstetric hemostasis is begun.

Chemotherapy should also be listed as an adjunct to the treatment of placenta previa. At the present time both chemical agents and antibiotics are administered prophylactically in cases in which there has been much vaginal manipulation. Unless there is a history of sensitivity to the drug, patients treated by cesarean section often receive 5 Gm. of sulfathiazole intraperitoneally. If complications develop in the postpartum period, chemical and antibiotic agents have an important position in treating them.

Results

Maternal.—Two mothers lost their lives as a result of placenta previa in this series. This gives an incidence of 1.5 per cent. A summary of these cases follows.

CASE 1.—The patient, aged 24 years, gravida ix, gave a history of repeated stillbirths. General examination, including special studies for syphilis, gave negative results. She had slight painless vaginal bleeding at the twenty-sixth week of pregnancy. She was admitted to the hospital on Aug. 3, 1925, at the twenty-eighth week of pregnancy, in labor and with profuse vaginal bleeding. Vaginal examination revealed that the placenta covered two-thirds of the cervical os. The membranes were ruptured and a version and extraction done; a stillborn infant weighing 1,814 Gm. was delivered. The placenta was removed manually. Immediately after this procedure the patient died suddenly on the delivery table. There were no notes in the records regarding transfusions or intravenous use of fluids. Autopsy revealed only ascites and hydrothorax. There was no rupture of the uterus.

15 per cent of the incomplete varieties. Factors which influenced the decision to perform section in the thirteen cases of other types of placenta previa were age, parity, physical condition, hemorrhage, an unfavorable condition of the cervix, position and presentation of the fetus, questionably normal pelvis, and particularly important fetuses (such as in elderly primiparas). Cesarean section was employed twice after use of a bag had failed to control the bleeding. One section was employed because of hypertension, and a lowlying placenta was an incidental finding. The uterus was routinely packed with iodoform gauze after cesarean section.

Sixty-two, or 46 per cent, of the patients received other forms of treatment than abdominal delivery. In 28 patients, rupture of the membranes sufficed to control the bleeding. A Voorhees bag was used 17 times. Usually the largest bag that could be introduced through the cervix was chosen. It was inserted intraovularly 15 times, and extraovularly twice. Ten patients were treated by version and extraction, of whom two underwent a Braxton-Hicks version after perforation of the central placenta previa; in the other eight patients, the cervix was more than three-fourths dilated when the version was done. Extraction was never performed until complete dilatation of the cervix was attained. Five patients were treated with a bag and subsequent version and extraction. A Willett forceps was used once after use of a bag. This type of scalp traction is effective in the control of bleeding, and has been used more frequently in the past two years. Its use has been favored by certain authors,¹⁴ but decried by others.¹⁰

The management of the third stage of labor after placenta previa is important, yet it is seldom stressed in the literature. When a patient has already experienced hemorrhage as a result of an obstetric complication during the first and second stages of labor, the obstetrician must be more alert and active in the treatment of third stage bleeding. Abnormal location of the placenta may lead to incomplete separation, and there may be bleeding from the trauma of delivery procedures.

In Table IV it is shown that 87 of the 134 patients had spontaneous deliveries of the placenta, and 35 underwent removal of the placenta according to the usual technique in a cesarean section. It was found necessary in 12 of the 99 cases of vaginal delivery to remove the placenta manually to control hemorrhage. Invasion of the uterus carries a well-recognized risk, but such risk is far less dangerous than continued blood loss.

TABLE IV. MANAGEMENT OF THE THIRD STAGE

MANAGEMENT	PLACENTA PREVIA, TYPE				TOTAL (134 CASES)	
	LOW-LYING	LATERAL	PARTIAL	CENTRAL		
					CASES	PER CENT
Spontaneous delivery	22	8	54	3	87	65
Manual removal			10	2	12	9*
Cesarean section	1	1	11	22	35	26
Uterine packs	2	3	17	3	25	19†
Postpartum hysterectomy			1		1	1

*Nine per cent of total cases or 12 per cent of vaginal deliveries.

†Nineteen per cent of total cases or 25 per cent of vaginal deliveries.

Hemorrhage continued after the placenta was delivered in 25 cases. In these instances, the uterine cavity was explored for retained fragments or possible rupture and was then packed with iodoform gauze. This procedure has fallen into some disrepute in recent years, but we continue to obtain excellent results by its employment when oxytocics and fundal compression fail to control

TABLE VI. FATE OF THE INFANTS

WEIGHT OF INFANT, GM.	TOTAL BIRTHS	STILL-BIRTHS	NEONATAL DEATHS	SURVIVALS	
				NUMBER	PER CENT
Below 1,000	3	2	1	0	0
1,000 to 2,500	57	12	9	36	63
2,500 or more	81	8	0	73	90
Total	141	22	10	109	77
Per cent of total births		16	7		
Gross fetal mortality, per cent			23		

TABLE VII. TYPE OF TREATMENT AND FETAL MORTALITY

TREATMENT, TYPE	TOTAL BIRTHS	INFANTS STILL OR PREVIALBLE*	STILLBIRTHS	NEONATAL DEATHS
No treatment	39	7	1	6
Ruptured membranes	31	2	5	1
Voorhees bag	18	2	4	2
Version	10	4	7	
Bag and version	5	2	2	
Bag and Willett forceps	1			
Bag and breech extraction	1			
Cesarean section	36		3	1
Total	141	17	22	10

*Condition of infant at time treatment was started.

DeLee and Greenhill, and others have emphasized that fetal anomalies are numerous in pregnancies associated with placenta previa. In this series there were two infants who had anomalies incompatible with life, and five infants who had less serious anomalies. This gives a total of seven cases, or 5 per cent.

Discussion

There is fair agreement as to incidence, parity, classification, increased number of malpresentations, and other general factors in many of the papers on placenta previa in the past ten years. There is also agreement as to the risks of the condition and as to the importance of generous use of blood transfusion in treatment. However, there is difference of opinion as to its active management.

Johnson of Texas, Ekas of New York, and Macafee of England have pleaded for conservative management of this condition. These authors have stated that they do *not* think that it is always necessary to treat placenta previa at the time of the first hemorrhage, although they advise hospitalization. In the series herein reported, delay in treatment may have been a contributing factor in both maternal deaths. We feel that delay increases blood loss, the anemia, and the danger of infection. We justify delay only when the fetus in the particular case in question is of more than usual importance, such as in the case of a woman with a previous long period of infertility. Seeley, Schumann, and Adair have all pointed out the hazards of delay.

There is a fairly large group of obstetricians who favor dividing the treatment of placenta previa into two categories; namely (1) that of doing nothing or simply rupturing the membranes, and (2) that of doing a cesarean section. The advocates of this approach to treatment include Daichman and Pomerance,

In retrospect, it seems that if this patient had been investigated and treated at the time of her initial bleeding, she might have been saved. Also, when she was admitted with profuse bleeding, it appears that transfusion should have been started before vaginal examination was done.

CASE 2.—A patient, aged 43 years, gravida i, was admitted to the hospital on July 9, 1933, at the thirty-fourth week of pregnancy. She had had repeated episodes of slight painless vaginal bleeding since the twenty-sixth week of pregnancy. The fetus was in breech position, and a central placenta previa was diagnosed by rectal examination. No vaginal examinations were made. A classical cesarean section was done, with delivery of a living infant weighing 2,216 Gm. Central placenta previa was verified at operation. The mother had a stormy postoperative course, with a high fever, and died on the third postoperative day from paralytic ileus and peritonitis. Permission for autopsy was not obtained.

This case also demonstrates the danger of delay in treatment after initial symptoms have developed. It can be presumed that the repeated vaginal bleeding in this case was partially responsible for the subsequent infection. Whether modern-day chemotherapy and the administration of antibiotic agents would have altered the prognosis in this case is impossible to determine.

On the basis of the standard for morbidity of the American Committee on Maternal Welfare, in 27, or 20 per cent, of the cases morbidity occurred. In 17 cases morbidity followed cesarean section, and in 10 it followed vaginal delivery. Endometritis and parametritis did not occur in patients who underwent cesarean section. It is interesting to note that seven patients, or 5 per cent, had thrombophlebitis, the most common cause of morbidity in our series. Of these, two had nonfatal pulmonary emboli. Thrombophlebitis followed cesarean section four times and vaginal delivery three times. The incidence of thrombophlebitis was also high in the series of Davis and Campbell, and Ekas. The exact physiologic reason for this complication is not known, except for the increased incidence of thrombosis with any infection or anemia or both, and the lower location of big veins and sinusoids at the placental site. The other 20 patients had morbid conditions as follows: endometritis, four; parametritis, one; infection of the urinary tract, one; infection of the upper part of the respiratory tract, two; "caked" breasts, one; transfusion reaction, one; and undetermined conditions, ten. Very likely many of these ten represented mild instances of uterine infection.

Fetal.—Although most of the attention is directed toward the mother in cases of placenta previa, the outcome for the fetus is important. This is increasingly true, since the maternal mortality rates from placenta previa have approached zero.

The gross fetal mortality was 23 per cent, or 32 of 141 infants (Table VI). These statistics have not been corrected for prematurity, congenital anomalies, or intrauterine deaths, as in all these conditions the placenta previa itself may be wholly or in part the etiologic factor in the fetal loss. One must always regard "corrected" fetal mortality rates in placenta previa with caution.

Table VI shows an increasing number of surviving infants as weight increases. However, when fetal mortality is correlated with the type of treatment, few conclusions can be drawn. It would seem from Table VII that version and use of a bag offer a poorer prognosis to the fetus than section. However, the table also shows that one of the determining factors in electing the course of treatment was the condition of the fetus. The chances of the fetus were known in advance to be nearly hopeless in 17 instances. When one considers that 80 per cent of the patients with placenta previa are seen before term (Table II), it is surprising that the infant survival rate is as high as it is.

these factors have not entirely solved the problem of thrombosis. Various methods to combat thrombosis have been used extensively in surgical conditions with fairly good results. Perhaps some of these methods, notably the use of anticoagulants, should be given a more thorough trial in obstetric complications.

TABLE VIII. REPORTS FROM RECENT LITERATURE

AUTHOR AND YEARS COVERED	CASES	PLACENTA PREVIA, PER CENT	PER CENT			TYPE OF TREATMENT, PER CENT		
			MATERNAL MOR-TALITY	MATERNAL MOR-BIDITY	FETAL MOR-TALITY	NONE	VAGINAL	SECTION
Morgan 1937-1944	130	1.6	0		36	17.8	46.1	36.1
Ekas 1927-1943 (?)	86	0.6	2.3	40	55.8	41.8	53.6	4.6
Barrett 1938-1944	102	0.76	3.9					
Johnson 1939-1944	79	0.32	0		31.7	36.7	10.1	53.2
King and Chun 1936-1941	134	0.78	0.75		54			13.4
Ransom 1934-1943	215	0.8	0.93		22.3			
Seeley 1933-1942	250	0.78	2.8	31.2	34.6	23	53	24
Williamson and Greeley 1932-1944	162	0.4	3.1	58.4	31.1			47.5
Macafee 1937-1944	174		0.57		23.5	4	57	39
Scott 1928-1944	191	1.19	2.6		29.6			
Davis and Campbell 1931-1945	325	0.79	0.6	22.1	31.6	28.6	27.4	44
Daichman and Pomerance 1935-1946	165	0.43	0.6	41.2	25.8	12.7	27.8	59.3
Mayo Clinic 1918-1945	134	1.12	1.5*	20	23	28	46	26
Average		0.80	1.51	35.5	33.2	24	40.1	34.7

*One death occurred in 1925 and the other in 1933.

Summary

Placenta previa continues to be one of the more serious complications of pregnancy. A series of 134 cases occurring over a period of twenty-seven years is reported in this paper, with a maternal mortality rate of 1.5 per cent, a maternal morbidity rate of 20 per cent, and a gross fetal mortality rate of 23 per cent. The treatment in each case has been individualized according to the multiple factors present at the time of entry of the patient into the hospital. Although cesarean section has not been held in reserve, a greater than average number of patients have been treated by various vaginal manipulations without added fetal risk, and, to date, with maternal safety. The generous use of blood transfusion has contributed to the low morbidity and mortality rates. The complications of thrombosis and thrombophlebitis stand out as causes of maternal morbidity.

Scott, Watson, Taylor, Barrett, and Cosgrove. In our series, the patients were treated by multiple methods, and the incidence of cesarean section was below the average reported in the literature.

From what has been said, it probably is evident that we do not consider cesarean section the routine treatment for hemorrhage from placenta previa. Often hemorrhage can be controlled by skillful vaginal manipulation; the "art of obstetrics" has a place in the management of the condition. Yet, there seems to be a trend at present to resort to cesarean section when confronted with almost any obstetric difficulty. DeLee* deplored this trend when he said that the tendency was to "cut" obstetric "knots" (by cesarean section) rather than patiently and skillfully to unravel them by the art and techniques of obstetrics. Admittedly, cesarean section usually is the easiest way out of difficulties for the attendant. In spite of the greatly enhanced maternal safety of cesarean section, it may be too optimistic to say that cesarean section is the best treatment for the condition or for the patient. The obstetric future of the patient as well as the immediate problem must be considered. The risk of repeated cesarean sections and the resulting limitation on the number of future pregnancies are factors which cannot be disregarded. As far as our own experience, herein related, reveals, our maternal and fetal mortality rates have not increased over the years, through which our attitude toward cesarean section for placenta previa has remained conservative.

In our series, treatment which was thought to fit was chosen in each case, taking into consideration the factors of age, parity, general physical condition, duration of pregnancy, estimated size of the fetus, amount of bleeding, the condition of the cervix, adequacy of the pelvis, position and presentation, and so forth. We have continued to employ the various vaginal procedures of use of a bag, version, Willett forceps, and often a pack in the uterus after delivery of the placenta. Blood has been given generously by transfusion. In recent years, antibiotics have been used both for prophylaxis and therapeutics. Thus, in this series we find a greater than average use of vaginal procedures and a less than average use of cesarean section (Table VIII). The maternal morbidity and mortality rates in this series justify the principles of treatment outlined above. In addition, the fetal salvage compares favorably with that of those who advocate the more liberal use of cesarean section. Matthews and Seeley also have advocated individualization of treatment.

In regard to maternal morbidity, thrombophlebitis seems to be the most important consideration. Infection predisposes to thrombosis, and reduction in morbidity from infection may be expected from the use of antibiotics. Anemia is another contributing factor to thrombosis. Barker and co-workers found an increased incidence of thrombosis and phlebitis in patients whose value for hemoglobin was below 12 Gm. per 100 c.c. of blood. It is probably best to administer blood by transfusion to obstetric patients undergoing hemorrhage, so that when they enter the puerperium the value for hemoglobin will be above 10 grams. But

*In order to represent this great deceased obstetrician fairly however, it should be noted that at the time of his death he favored relatively frequent use of cesarean section in placenta previa.

CERVICAL PREGNANCY

A Report of Two Cases and a Discussion of the Treatment

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CERVICAL pregnancy is a comparatively rare type of ectopic gestation which is of special interest because of the lack of knowledge regarding its etiology, the difficulties in making a correct diagnosis, and its high mortality. In the February, 1945, issue of the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, Studdiford published a fairly comprehensive review of the literature; he found 14 certain cases, 14 probable cases, and added two probable cases of his own. The *Index Medicus* lists a few references (case reports) in addition to those quoted by Studdiford, and at least two cases have been reported since his review, one by Bowles and one by Fearl. Numbers of others must go unrecognized or unreported. Within the last several years I have encountered two cases, one a "probable" case and the other one a proved case, because surgical intervention was demanded and provided us with the pathologic proof. Studdiford's article contained an excellent review of the symptoms, signs, and basic pathology of the condition. I wish to report my two cases in order to underline the potential dangers of cervical pregnancy, because one of the cases is such a good pathologic demonstration of the condition, and because of the therapeutic considerations which these cases brought up.

CASE 1.—J. M., No. 118199, aged 26 years, para i. The patient was first seen because of sterility of ten months' duration. She had had one normal spontaneous delivery at term three years previously. Her past history was entirely irrelevant. Menses began at 11 years of age, and came every 26 days for five days. Examination revealed a slim, healthy-appearing young woman. She was entirely feminine and presented no evidences of glandular imbalance. Heart and lungs were negative. The abdomen was negative. The pelvic organs were entirely normal except for deviation of the uterus to the left, perhaps due to a small scar in the left fornix, continuous with an old cervical laceration. The patient was advised to temporize. Six months later, on June 28, 1945, the patient had what she interpreted as a normal menstrual period. About one month later, on July 24, she began to have spotting from the vagina which continued for five days, then stopped. After another week, frank bleeding began and continued daily for four weeks. There were no cramps. Other signs of pregnancy were present, such as breast fullness and slight nausea. She was not examined at this time. It was assumed that the patient was aborting. Ergotrate produced neither more nor less bleeding. A few days later the patient passed a number of clots and some tissue, she thought. Bleeding ceased for two weeks, at which time a vaginal examination was made. The external os was found to be dilated 2 cm. and obliterated. Lying in the cervical canal was a mass of placental tissue. The uterine body seemed about normal in size and retracted above the cervix proper. My impression was that this represented the cervical stage of an abortion. I thought that the uterus had expelled its contents into the cervix, which had ballooned out to accommodate them. The

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masses were palpable. Speculum examination revealed a large bluish cervix. The os was not dilated, and there was a small amount of blood in the vaginal canal. No placental tissue was visible. A tentative diagnosis of incomplete or threatened abortion with endometritis and pelvic peritonitis was made. Cervical cultures were taken and showed hemolytic streptococci. Laboratory examination revealed: hemoglobin 70 per cent; white blood cells 9,250, and normal urine. Wassermann was negative. The patient was given penicillin and bed rest. She remained in the hospital for ten days during which time she received a transfusion of 500 c.c. of whole blood. Temperature was normal after the third hospital day. Only a minimal amount of bleeding occurred.

Twenty-four days later, on Oct. 15, 1946, the patient was readmitted to the hospital with the following story: After leaving the hospital she remained asymptomatic until one week prior to readmission, at which time she developed more vaginal bleeding and abdominal pains. This continued intermittently. For the last twenty-four hours she had passed large clots and felt feverish. Examination revealed the patient to be slightly pale, talkative, and quite apprehensive; temperature 103.2° F. orally, pulse 132, blood pressure 120/70. Laboratory examination: hemoglobin, 65 per cent; 1 plus acetone in urine. Speculum examination showed a moderate degree of cervical dilatation. Protruding from the external os there appeared to be products of conception. These were gently removed by means of sponge forceps, and found to consist of a macerated fetus (length, 32 cm.). Immediately thereafter there was a profuse hemorrhage which could not be controlled by uterine massage and parenteral Ergotrate (both intramuscular and intravenous). The lacerated umbilical cord broke, and no attempt was made to remove the placenta, as the patient was rapidly going into shock. Immediately the vagina was packed and 2 units of plasma were given intravenously; within the next 45 minutes 1,500 c.c. of whole blood were administered. Gradually the patient responded and by morning the blood pressure had risen to 92/60 and the pulse had stabilized at 120. There was no bleeding through the pack.

It was deemed advisable to remove the uterine pack the following morning, and if no bleeding recurred an attempt was to be made to remove the placenta. Under cyclopropane anesthesia the pack was removed. Since there was no immediate bleeding, 2 fingers were introduced into the patent cervix, where the lower edge of the placenta could be felt. On manipulating the placenta so much bleeding occurred that no further attempt was made to remove it. Five minims of Pitocin in 20 c.c. of saline were given intravenously and the fundus massaged; however, profuse bleeding persisted. The uterus was then packed tightly with gauze. Total blood loss at this time was measured at 2,600 c.c. The patient was in profound shock again and a transfusion was started immediately. She received four transfusions within the next twelve hours.

On October 17 (i.e., 24 hours later) a second attempt was made to remove the uterine pack very gradually. Before this could be completed profuse bleeding recurred, measuring 1,900 c.c. The uterus and vagina were repacked and three transfusions were given. The correct diagnosis had not been made at this time; however, it seemed obvious that the bleeding could not be controlled vaginally and that a hysterectomy would have to be attempted. Within five hours of the last episode of bleeding the patient's blood pressure had risen to 90/60, and her pulse rate was 126. It was thought that her condition was good enough to permit laparotomy. Under cyclopropane anesthesia the abdomen was opened, with the following findings: The uterine body itself was only slightly enlarged and was perched on top of a large distended mass which was interpreted as the lower uterine segment markedly distended with packing and placental tissue. This distended mass was at least 9 cm. in diameter. Its anterior wall was soft, seemed rather thin, and contained many large distended veins. The uterine pack was slowly withdrawn from below in order to reduce the volume of the mass and permit an approach to the vessels. Dissection was carried down on either side of the uterus to the level of the uterine arteries. The cervix of the uterus could not be identified as such and it now became apparent that it was incorporated in the large soft mass. It was

patient was advised to enter the hospital for the completion of the abortion. This she did on Sept. 11, 1945. Her hemoglobin at this time was 87 per cent (12.9 Gm.), blood pressure 120/55. Under Pentothal anesthesia the cervix was exposed and the placental tissue was grasped with an ovum forceps for removal. Some of it came away easily, but a considerable amount of tissue could be removed only by pulling it forcibly. This resulted in profuse bleeding, the origin of which appeared to be the posterior wall of the dilated cervix. Digital palpation of the interior of the cervix revealed a cavity about 3 to 4 cm. in diameter, a very soft, thin, and ragged posterior wall, the internal os at the top of this cavity, no bigger than lead-pencil size. It was at this time that a diagnosis of cervical pregnancy was made. The cervical cavity and the vagina were tightly packed with gauze and the patient was returned to her room. The packing was removed the next day, but resulted in so much bleeding that it was necessary to repack immediately. A 500 c.c. transfusion was given at this time. On the following day, Sept. 14, 1945, the hemoglobin had dropped to 70 per cent (10.1 Gm.). A second attempt was made to remove the packing very gradually. The patient did not bleed very much at first, but by the next day was soaking pad after pad and looked very pale. Hemoglobin at this time was 66 per cent (9.7 Gm.). The cervix was exposed and incised transversely with the idea of clamping or suturing the bleeding area directly. This was not very satisfactory. Finally the canal was packed with fibrin foam and transfixed with a figure-of-eight suture. Bleeding ceased. No gauze packs were inserted. The patient received two transfusions of 500 c.c. each that day, and another one two days later. A week passed with only vaginal spotting, then profuse bleeding started again and required repacking with fibrin foam and gauze. It was then decided to take the patient to surgery the next day, and if definite and satisfactory hemostasis could not be achieved vaginally, hysterectomy was to be resorted to. The patient was transfused with 500 c.c. of whole blood. The cervix was exposed; very little bleeding occurred. There had been definite shrinkage of the organ and undoubted thrombosis of vessels. My efforts were confined to approximation of the lateral incisions which had been made at the previous operation. The restoration of the cervix and effective hemostasis were thus accomplished. The patient received her sixth and seventh transfusions during the next few days. No further bleeding occurred, and the patient was discharged from the hospital in good condition ten days later. Two days before discharge her hemoglobin was 82 per cent (11.9 Gm.). Subsequently the patient became pregnant again and delivered spontaneously at term without difficulty.

Though there appears to be little doubt of the correctness of the diagnosis, this case must be labeled as "probable," since we have no absolute proof. Fortunately, the pregnancy terminated at an early stage, and fortunately, too, it was possible finally to achieve hemostasis without resorting to hysterectomy. It followed the pattern described by Studdiford for other cases in which there was an early termination of the pregnancy. In the majority of these instances it has been possible to control the bleeding without hysterectomy, although, in many hemorrhage of alarming proportions has occurred before the final control. Tight packing of the area, probably of much longer duration than was allowed in the case reported, would seem to be of great importance.

CASE 2.—V. B. The patient was a 28-year-old white, separated, office worker, gravida ii, para 0, who first entered the San Francisco Hospital on Sept. 12, 1946, with a chief complaint of cramps and vaginal bleeding of one day's duration. The patient's last regular menstrual period had occurred on May 23, 1946, and was normal in duration and amount. She had had morning nausea and breast tenderness during the three months prior to entry to the hospital. Otherwise, the course of her early pregnancy had been uneventful. On Sept. 10, 1946, the patient had a sudden gush of blood from the vagina and experienced abdominal cramps.

On her admission to the hospital, the temperature was 102° F. orally, pulse 110, blood pressure 120/70. She appeared in good general condition without evidence of shock. Examination of the abdomen revealed generalized tenderness especially over the lower quadrants. No

and intact except for a small rent in the posterior wall at the external os. In the region immediately above and anterior to the cervical os there was a large, round, firm mass some 8 cm. in diameter which was thought to be the remains of the cervical body distended by the placental tissue which had not been removed at surgery. Because the patient had passed no placental tissue since surgery and the external os was now very small and bleeding was continuing, it seemed advisable to attempt removal of the remaining cervical stump with its contents.

Consequently, on November 22, the patient was taken to surgery again. A second laparotomy was performed, and at this time it was found that the cervical stump was still very large, being distended and filled by large pieces of old placental tissue. Because of the inflammatory induration about the cervix and the intimate adhesion of the overlying bladder anteriorly and the bowel posteriorly, it was deemed advisable simply to evacuate the cervix and close it without further operative procedure. The cervix was opened at its superior aspect and the placental tissue removed by sponge stick until the entire cavity appeared free of visible placenta. The top of the stump was resutured and the abdomen closed. The patient made an uneventful recovery without further bleeding. She was discharged from the hospital on her fourteenth postoperative day after the second laparotomy, or a total of 53 days after the initial surgery. During her hospital stay the patient received 11,000 c.c. of whole blood.

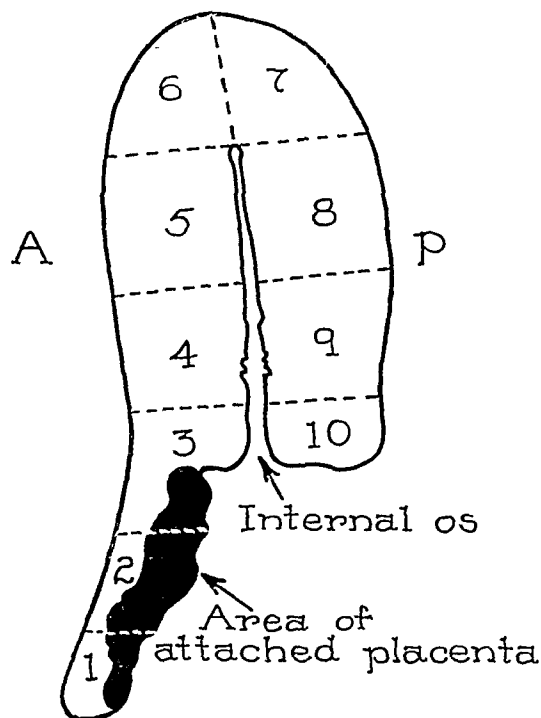


Fig. 2.—Blocks were cut from a 3 mm. thick slice of tissue taken from the sagittal plane as indicated in this diagram. Confirmatory blocks were also cut in adjacent planes.

Pathologic Report.—The specimen consists of the enlarged, intact uterine body which has been amputated through its posterior wall just below the level of the internal os. In other words, the anterior wall of the corpus is continuous inferiorly with a flaplike projection of tissue extending down from the region of the internal os, presumably the thinned out cervical wall. Only the outer 3 mm. of this projection is composed of the usual fibromuscular layers; the remainder of its thickness varies from 0.5 to 1.0 cm. and is composed of dark friable tissue resembling placental tissue. The latter tissue reaches to within 1.5 cm. of the internal os superiorly, and appears to have been cut off with the cervical wall, which does not include the external os inferiorly. The drawing and the diagram illustrate these findings perfectly.

not until this time that the diagnosis of cervical pregnancy was made. Although not much bleeding had occurred upon removal of the pack, it was not possible to carry the dissection low enough to remove the entire cervix because of the volume of the mass which almost completely filled the pelvis. It was necessary to amputate the uterus at an undetermined point in the cervix as low as could be reached. In cutting across it, placental tissue was also incised. Fortunately, the sutures closing the friable cervical walls sufficed to control immediate hemorrhage. It was hoped that the remaining placental tissue would separate and be expelled spontaneously.



Fig. 1.—Posterior view of the amputated uterus. The internal os (O) is clearly visible. Placental tissue (P) attached to the greatly elongated and thinned out cervix comes to within $1\frac{1}{2}$ to 2 cm. of the os.

The postoperative course was morbid up to the fourth postoperative day, when the temperature fell to normal. Patient received an additional 2,500 c.c. of blood on the day of her laparotomy, 200 c.c. the following day, and an additional 1,000 c.c. on the third postoperative day. By the fifth postoperative day the hemoglobin was 9.4 Gm. An additional transfusion was given on the sixth postoperative day and the hemoglobin rose to 10.8 Gm. On the ninth postoperative day a small amount of vaginal bleeding recurred. A small pack was placed in the remaining portion of the cervix and removed after twenty-four hours with minimal bleeding. On the fifteenth postoperative day more bleeding occurred; an Oxyeel pack was placed in the cervix and seemed to control the bleeding. The patient was given additional blood during this period. A moderate amount of vaginal bleeding persisted intermittently. Vaginal examination on the thirty-fourth postoperative day revealed the cervix to be soft

A sagittal section of tissue was removed from the midline area and cut into blocks, as indicated in Fig. 2, so that a microscopic survey of the entire uterus could be made in this plane. The sections revealed that the corpus was lined by a thin layer of endometrium exhibiting little or no decidual response, but showing some diffuse inflammatory reaction, most marked near the internal os. There were no evidences of placental fragments, neither villi nor chorionic cells, in the body of the uterus. Sections from the flap of tissue below the internal os showed placental tissue, both well preserved and degenerated, beginning at the point on the anterior cervical wall 1.5 cm. below the internal os, extending down to the cut margin, and implanted on a very thin layer of fibromuscular tissue. There was no definite decidua between placenta and cervical wall. Cervical glands could not be identified in the sections taken. Numerous large blood sinuses underlay the placenta, and there was a spotty inflammatory reaction near the areas of partial placental separation. *Diagnosis:* Cervical pregnancy with partial separation.



Fig. 5.—Section from block No. 4 as indicated in Fig. 2. A considerable leucocytic infiltration is present. No frank decidual reaction is visible.

Comment

Fortunately, cervical pregnancy is rare, because it is an extremely dangerous condition—there was a 20 per cent mortality in Studdiford's cases. Much of the danger arises from the fact that it is difficult to make a diagnosis before procedures have been instituted which may result in massive hemorrhage; i.e., specifically, attempts to remove the placenta. The frequency of abortion, with which it is usually confused, and the rarity of cervical pregnancy combine to dull one's diagnostic acuity. If one should happen to have an opportunity to examine the patient before some separation of the placenta and bleeding had occurred, ballooning out of the cervix above a flattened-out cervical canal and external os would constitute the significant findings. If the pregnancy should have progressed beyond the first three or four weeks, the

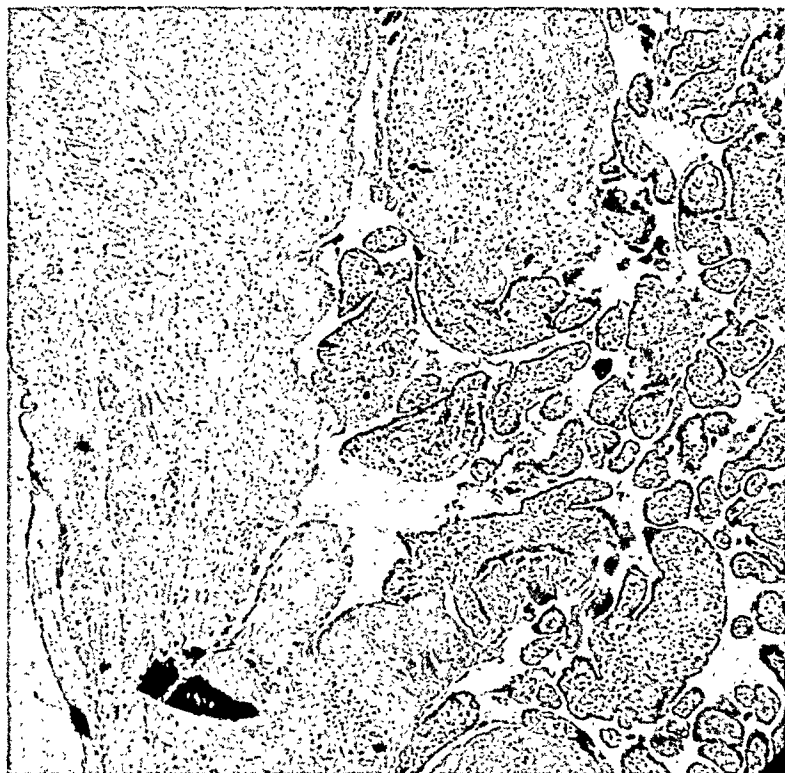


Fig. 3.—Section from block No. 1 as indicated in Fig. 2. The thinness of the cervical wall is well illustrated. No cervical glands are seen.



Fig. 4.—Section from block No. 3 as indicated in Fig. 2. This is the uppermost margin of the placental site, and it lies below the internal os.

UTERINE DYSTOCIA*

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THERE is no need of defining dystocia to a group of obstetricians and general practitioners. We all have had enough experience with painful or slow labors to understand what the term means. Mechanical dystocia, due to cephalopelvic disproportion, malpositions, short cord, etc., has always overshadowed other forms of dystocia in our thinking and teaching, probably because a contracted pelvis or an oversize baby is easy to recognize and the mechanics of such obstruction is easy to understand. This type of dystocia is becoming relatively less important for the reason that marked pelvic deformities are rapidly disappearing. This is especially true in private practice, but even in the clinic population, nutrition has improved so greatly that a rachitic pelvis has become a rarity. Our thanks are due to the public schools for this great improvement. For instance, a survey of the school children in Richmond several years ago showed a smaller percentage of undernourishment among the Negro children than among the whites. The schools that showed the most undernourishment were in the so-called best neighborhoods. The explanation that was advanced was that the poor children did what the teacher told them to do but the rich children and their parents knew better.

I wish to discuss at this time dystocia caused by dysfunction of the uterus. The slow, difficult deliveries due to faulty uterine contractions have long been recognized.

Paulus Aegineta¹ (626-690) in the seventh century taught that "difficult labour arises either from the woman who bears the child, or from the child itself, or from the secundines, or from external circumstances. From the woman in labour, either because she is gross and fat, or because her whole womb is small, or because she has no pains, or is affected with fear, or because the uterus or some other part is inflamed or otherwise diseased, or because, from some natural weakness, she is unable to expel the foetus, or because the labour is premature." Smellie² clearly understood that various parts of the uterus could contract irregularly. Dewees³ called this condition partial contractions of the uterus. Other terms that have been used are strictures of the uterus⁴ and irregular or spasmodic action.⁵ Recently, Jeffcoate⁶ described these conditions under the term "incoordinate uterine action." It seems to me that uterine dystocia is a better term. It includes several related conditions to which various names have been attached: inertia, uterine dyskinesia, dystocia dystrophia, hourglass contraction, and constriction ring.

I became interested in constriction rings in 1924⁷ when Dr. James Garber of Birmingham, in commenting on my paper, "The Action of Adrenalin on the Pregnant Human Uterus," said that the drug ought to be good for constriction ring. I have confined my talking and writing to constriction ring dystocia, because it was a definite condition that I could feel and be certain

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body of the uterus might possibly be palpable above the ballooned-out cervix, simulating a fibroid at the fundus, of the "monkey-cap" variety. If, as is usually the case, some bleeding has already set in, then of course the similarity to threatened or incomplete abortion is great. It appears that the products of conception are not expelled with as much dispatch as in the usual abortion, however. This is readily understood when we reflect that the force of uterine contractions is absent; we have to deal with the relatively passive and scanty cervical musculature. Thus, undue delay in the completion of abortion should put us on guard. At this point, conditions may now prevail which may very much suggest the cervical stage of an abortion; it may well appear that the uterus has expelled its contents into the cervix which has gradually become ballooned out to accommodate them—and there they have been retained, with perhaps slight or moderate intermittent serous discharge and bleeding. Forceful removal of even a small portion of the placenta in the early stages of the process usually results in copious hemorrhage. This undesirable result is easily comprehended when it is realized that there is no muscular mechanism in the cervix designed to clamp off the subplacental blood sinuses at separation, as there is in the corpus. Naturally, the more advanced the pregnancy, the more copious the bleeding is likely to be.

Every effort should be made to make the diagnosis before any manipulation is undertaken. Separation of the placenta should be avoided, and indeed the placenta might profitably be tightly packed against the cervical wall, particularly if there has been a partial separation. Thrombosis of vessels and gradual absorption should occur in just the same manner as they do with a placenta left in the peritoneal cavity after an abdominal pregnancy. The placenta implanted in the cervix should not be disturbed any more than should the placenta implanted upon bowel and its mesentery. Finally, at removal, preparations for immediate transfusion and repacking should be at hand, since exsanguination may occur in a very short period of time. It is possible that in time the placental tissues would be absorbed completely.

As a number of the reported cases indicate, bleeding may be so difficult to control that hysterectomy is demanded. Often this is unfortunate because of the youth of the patient; it can probably be avoided in the majority of the early cases. With more advanced pregnancies there is far more likelihood that hysterectomy will be demanded eventually.

Obviously, the ability to manage cases of this kind successfully, particularly when recognition has been delayed and hemorrhage has been great, depends upon the availability of blood in large amounts, and an alert hospital staff.

It is hoped that the report of these cases and the airing of the views I have acquired from my experiences with them will assist in making some others alert to this very trying condition, and will help to guide them should they encounter such a case.

years ago, when I recorded on a kymograph variations in intrauterine pressure every time I used a Voorhees' bag, I noticed frequently that small contractions of 5 or 10 mm. Hg pressure would dilate the cervix rapidly in some cases, whereas, in other cases, particularly in premature cases, strong contractions of 40 to 50 mm. of Hg had little or no effect on the cervix. More recently, the group at the University of Georgia⁹ has studied this more carefully. By introducing balloons at various levels in the cavity of the uterus they have shown that both the pregnant and nonpregnant human uterus may contract in an orderly or in a disorderly manner. They have actually demonstrated a constriction ring in a nonpregnant uterus. If the contractions are coordinated, the contents of the uterus, be it fetus, ovum, or blood clot, are expelled, but if the contractions are uncoordinated the uterine contents remain stationary. On Jan. 30, 1948, at a Conference on Normal and Pathological Physiology of Pregnancy, S. R. M. Reynolds¹⁰ reported his work with external hysterography using a differential tocodynamometer. He also showed that the pregnant human uterus acted in various ways. It was only when the contractions of the fundus were stronger and longer than those of the midportion, and those of the midportion were stronger and longer than those of the isthmus, and those in turn stronger and longer than those of the cervix, that progress of labor was made.

Thus we have evidence obtained by laboratory methods that the uterus can and does act incoordinately and ineffectually. We have known this clinically for years, but it is nice to have scientific support for our clinical beliefs. Uterine dystocia may take various forms as already indicated and these forms are not necessarily fixed and constant. It may occur when there is no mechanical cause for a long and difficult labor or it may occur when the patient has some disproportion between the fetus and the pelvis. In other words, there are cases of purely uterine dystocia and cases of purely mechanical dystocia, and there are cases in which there is some disproportion and some uterine incoordination. When there is this overlapping of the two conditions, there is opportunity for the display of nice clinical judgment.

The effect on the course of labor is well described by Jeffcoate. Since my studies have been chiefly with the severer type, i.e., constriction ring dystocia, I quote from him lest someone might think my picture too pessimistic. Incoordinate uterine action, he says, "even to the extent of constriction ring formation, can occur during any stage of labor, before or after rupture of the membranes. In the third stage, the typical example is 'hourglass contraction' of the uterus. The general effect of incoordinate uterine action is to prolong the course of labour, especially the first stage. The cervix dilates slowly but after a distressing and long first stage may become fully dilated. In the common but less serious cases, and especially if the fetal head rotates favourably, the second stage may be normal and delivery spontaneous. If the disturbance of function is more severe, the woman is exhausted or the fetus is showing signs of distress by the time the second stage is reached and forceps delivery becomes necessary. This may be difficult, especially if a constriction ring persists or forms during the second stage. Quite frequently the cervix never really attains full dilatation and a 'rim' has to be slipped up over the presenting part before the forceps blades are applied. In the most serious cases the cervix may be only half dilated or less, even after several days of labour."

The etiology of this condition is obscure. Various causes have been advanced—bags, bougies, rupture of the membranes, oxytocics, malpositions, fear and anxiety on the part of the mother, etc. In 1946¹¹ I analyzed my

about. I have never implied that it is the only type of dysfunction of the uterus. Today most obstetricians will agree that it is the most exaggerated form, just as eclampsia is the worst form of the toxemias of pregnancy. We know that many of these rings are reversible, and will disappear in time, although some will persist even after death. We know that they may occur in the third stage of labor, when we speak of them as hourglass contractions, and we have reason to believe that they may occur early in the first stage of labor, before the cervix is sufficiently dilated to permit an exploration of the interior of the uterus, and so definitely diagnose a ring. In such an event, the differentiation between constriction ring and inertia is extremely difficult, or even impossible.

Similarly, a rigid cervix is something that can be felt. It may persist for hours and may seem to be the sole reason why the baby is not born, and yet when the uterus begins to contract in an orderly manner the rigidity disappears. I had a dramatic example of this a number of years ago. The patient was a 39-year-old multipara whom I saw in consultation. Several years previously, a general surgeon had amputated a portion of her cervix. When I saw her she was 36 weeks pregnant, her membranes had ruptured, and she had been having indifferent labor pains for over twenty-four hours. She had had a chill and her temperature had risen to 103 degrees. The cervix was rigid and undilated. Her doctor was at a loss as to what to do. I advised him to give her $\frac{1}{4}$ grain of morphine and $\frac{1}{200}$ grain of hyoscine, and go home and go to sleep, and not to blame the nurse if the patient delivered the baby *in bed. Sure enough that is just what happened. About 2:00 A.M. the patient* awoke, had two pains, and the baby was born before even the intern could get to her. I can recall only two cases where the rigid cervix would not dilate and where I felt that Dührssen's incisions were indicated. Those who consider cervical dystocia a distinct entity define it as difficult labor due principally to failure of the cervix to dilate and be effaced within a reasonable time despite frequent and forceful uterine contractions. Such a definition well describes many cases of constriction ring dystocia and it is quite possible that many cases would be considered constriction ring dystocia by one clinician and cervical dystocia by another. Sackett⁸ found cervical dystocia in 1.05 per cent of 8,213 confinements at the Woman's Hospital. It was the major cause of 13.4 per cent of 382 prolonged labors and the major indication for 9.5 per cent of 474 cesarean sections. Almost 6 per cent of the high forceps, 3.6 per cent of the midforceps, and 1.7 per cent of the low forceps operations were due to this syndrome.

Colicky pains, uterine inertia or atony, and uterine dyskinesia are less definite, or possibly I should say they have no definite physical signs. They may occur independently or they may alternate in the course of a single labor. Jeffcoate aptly says that the conditions have the same etiologic factors (primiparity, nervousness, posterior positions, etc.) and they require treatment on similar lines. For that reason he includes inertia among the incoordinate uterine actions.

Finally, a word about dystocia dystrophy. This pituitary disturbance produces definite signs. These heavy-set, short-fingered women are prone to have uteri that do not function well, but this is not invariably so. It should be considered a predisposing cause of uterine dystocia and not a form of that condition.

One is apt to assume that the efficiency of uterine contractions in labor depends upon their strength and duration, which in turn parallels the amount of pain felt. This, however, is far from the actual fact. Some twenty-five or more

good judgment both as to when and how the patient should be delivered, there is no reason for losing either mother or baby. The worst feature from the mother's standpoint is the time wasted while the cervix is dilating.

Treatment

The first essential in treatment of these tedious labors is to guard against the mother's becoming dehydrated and exhausted. She should be encouraged to drink liquids and eat simple food. Fruit juices are particularly valuable. If she does not take sufficient fluid by mouth, she should be given glucose solution intravenously or by rectum. Small doses of morphine are invaluable early in the first stage of labor. We have found magnesium sulfate (20 c.c. of a 10 per cent solution) given intravenously also helpful. After a rest, the "pains" are apt to become orderly and effective. In cases of pure inertia, Eastman¹⁶ and Reid¹⁷ advocate very small doses of Pituitrin repeated at 30 to 45-minute intervals until contractions become effectual. This treatment is recommended only in cases of primary inertia, a diagnosis that is sometimes hard to make. In a five-year period, there were 463 such patients at Johns Hopkins and in the same period there were 1,609 such patients at Harvard. In both clinics there was a great reduction in midforceps operations.

If the membranes have been ruptured for twenty-four hours, I have been in the habit of starting the patient on penicillin and continuing its administration until delivery. If the fetal membranes are opaque, indicating an amniotic sac infection, the penicillin is kept up for another twenty-four hours.

When the cervix is fully dilated or almost fully dilated, I am convinced that it is best for both the mother and child to effect a delivery. The patient is anesthetized and the whole hand is introduced into the uterus to determine if there be a constriction ring present. If a ring be found, it can usually be relaxed with 5 or 6 minims of Adrenalin hypodermically. The ring can be felt to relax in a few minutes, but sometimes it takes as long as a half-hour. Occasionally Adrenalin fails. In that case amyl nitrite might be tried. Recently I had a case in point.

The patient was a 30-year-old primipara, a former nurse, who consulted me on Feb. 17, 1947. At that time, her physical examination was normal. She gave a history of dysmenorrhea. She was due by Nägele's rule on September 29. In March, her blood pressure had risen to 140/80 and it remained elevated the remainder of her pregnancy in spite of a salt-poor diet. On September 6 it was 160/80 and she had a little albumin in her urine and slight edema of the ankles. On September 13, the blood pressure was 150/80 and the patient was nervous and irritable. Termination of pregnancy was advised. On September 24, the cervix was partly effaced and admitted 1½ fingers. Labor was induced by aminotomy. The patient began to have labor pains in seven and one-half hours. In two and three-quarters hours more, the cervix was completely dilated and the head was on the perineum, and in a right occipitotransverse position. Vaginal examination showed that there was still a rim of cervix encircling the head like a loose hat band. An attempt was made to apply Kielland forceps but was unsuccessful on account of a constriction ring. One-half c.c. of Adrenalin was given hypodermically but had no effect on the ring. A large wheal formed at the site of injection which may have been the reason that the uterus was unaffected. The dose was repeated one-half hour later with the same results. Most of this time the patient was under ether anesthesia. Her pulse was now 190 per minute. An ampule of amyl nitrate was broken in the ether mask and the anesthesia continued. The ring disappeared within two minutes. The forceps were applied without difficulty and an easy extraction was done. Just as I remarked, "There goes the ring," the anesthetist noticed that the patient's pulse had dropped to 90 per minute. The baby, a girl, breathed at once. She weighed 5 pounds, 13¼ ounces and

cases of constriction ring, which at that time amounted to 202. There were 102 cases in 7,354 induced labors, or 1.38 per cent, and 100 cases in 6,221 uninduced labors, or 1.6 per cent. When labor was induced by amniotomy, a constriction ring formed in 1.46 per cent of the cases, and when labor was induced by bags, a ring formed in 1.25 per cent. In 748 cases, small doses of Pituitrin were used before labor started or in the early part of the first stage and in these a constriction ring formed in 2.8 per cent of the cases. In 483 cases, the membranes ruptured spontaneously before labor began, and in these there was a constriction ring in 2.7 per cent. The average age of the patients who developed constriction rings was 28½ years which was more than two years greater than the average for the whole series of 13,575 cases. Only 30 had occiput anterior positions and more than one-half of the patients had a borderline contraction of the pelvis. In other words, these patients were slightly substandard obstetric risks. I have a feeling that the condition is a fatigue phenomenon. Such a theory certainly furnishes a good guide to the treatment.

Prognosis

The earlier writers reported high maternal and fetal mortality. The chief dangers to the mother are exhaustion, shock, postpartum hemorrhage, and infection, on the one hand, and injuries to the uterus, cervix, and vagina from attempts at delivery, on the other hand. The fetus may die from asphyxia, birth trauma, intrauterine pressure, or intrauterine infection. Dr. Edwin Rucker recently had an instructive case in this connection. It was a consultation case and an x-ray examination was done to rule out disproportion. The plate showed overlapping of the fetal skull bones which subtended arcs of different circles. The roentgenologists made a diagnosis of a dead fetus. The fetal heart tones were not heard. The patient was anesthetized and examination with the whole hand showed a constriction ring. The ring was relaxed with Adrenalin and the baby was delivered by version and extraction. He was easily resuscitated and left the hospital with his mother in good condition.

Rudolph¹² in his last report had a fetal mortality of 32 per cent and a maternal mortality of 3.5 per cent. In a former report¹³ he stated that the fetal mortality should be reduced to less than 15 per cent. Herman Johnson,¹⁴ whose idea in dealing with this condition is early diagnosis and prompt delivery, lost no mothers and had a fetal mortality of only 5 per cent in 105 private cases. My only fatal case occurred in my first twenty cases, before I had learned the value of Adrenalin. The patient was a Negro woman, the mother of 13 children, who was admitted to St. Philip Hospital after failed forceps and version elsewhere. The ring did not relax under deep chloroform anesthesia, and the fetus, which was macerated, was delivered by craniotomy. The mother did not recover from the anesthesia. In 1947,¹⁵ I reported my fetal results in detail. At that time I had had 216 cases with one set of twins. There was a gross fetal mortality of 19.3 per cent. In the last 150 cases the fetal mortality was 12 per cent. Since that report was written (1946) there have been 2,698 deliveries at the Johnston-Willis Hospital and deliveries at other hospitals conducted by Dr. Edwin Rucker, Dr. Hudson, or me, and in this number there were 54 with constriction rings. A ring was felt in each case. None was delivered by cesarean section. All 54 mothers and 54 babies survived. In view of our recent experience and now that penicillin is available for patients whose membranes have been ruptured for a long time, I feel that the prognosis is a great deal better, even in the worst cases. If one keeps up the fluid intake and the electrolytic balance and uses

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measured 20% inches. Both mother and baby made an uneventful recovery and left the hospital on the seventh day.

When the constriction ring relaxes, the patient should be delivered either by version and extraction or by forceps. The Kielland or the Luikart modification of Kielland's forceps is especially useful in this type of delivery. In other types of uterine dystocia, of course, there is no need of the Adrenalin or the amyl nitrite. Should you apply forceps without previously determining if there be a constriction ring, and you find unexpected resistance either to rotation or extraction the administration of Adrenalin will usually make the delivery an easy one. The question has been raised, Does the relaxation caused by Adrenalin predispose to postpartum hemorrhage? I have not encountered any such tendency, nor have I ever seen any ill effects from the use of Adrenalin. In an unanesthetized patient, Adrenalin will sometimes cause a disagreeable feeling of apprehension.

Subsequent Labors

I am under the impression that uterine inertia may recur at a subsequent labor, but I have never seen a constriction recur at a subsequent labor. Jeffcoate makes the statement that uterine efficiency improves with each pregnancy. "The prognosis for the second confinement depends largely on the degree of dilatation reached by the cervix in the first." If the child is delivered per vaginam, even if there be great difficulty, the next labor is more than apt to end in a spontaneous delivery. If, on the other hand, the child be delivered by cesarean section before the cervix has dilated, the next labor will probably be a difficult one.

Summary

The various forms of uterine dystocia are discussed. These vary from simple atony or uterine inertia to cervical dystocia and constriction ring. The type of incoordinate uterine action may vary from time to time in the same labor. The effect of these long labors upon the mother and baby is discussed, particularly when there is a constriction ring present. The best results for both mother and child are to be had by as prompt delivery from below as possible, i.e., when the cervix is dilated or almost fully dilated. If the patient is delivered by cesarean section before the cervix has dilated, the next delivery is apt to be difficult, although not so difficult as the first. A case is reported in which the constriction ring did not relax with Adrenalin and yet dramatically disappeared when amyl nitrite was used. In my last fifty-four cases with constriction rings, no baby was lost; the only mother lost in the entire series of 270 cases was before I began using Adrenalin in 1924.

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the deliveries performed by the authors plus all the patients delivered by two other members of the Glenville staff and all the cases of one member of Booth Memorial staff. The second group is made up of all the patients delivered by the remaining members of both hospital staffs.

Observation and Comparison

All of the patients were checked daily and recordings made with special reference to the mode of healing of the perineum from the day of delivery until the patient left the hospital. At the same time, a daily record was kept of each patient's highest temperature elevation, the amount and odor of the lochia, the general well-being of the patient, and the amount of pain originating in the perineum.

In Table I is recorded the highest temperature reading during the entire hospital stay of all the patients who were critically studied during the six-week period beginning June 15 of this year, 1948. By comparing the highest temperature elevation in the two groups of cases, it appears that there is no striking improvement in the temperature curve through the use of sulfathiazole locally in the vagina immediately after delivery. Although there are a few scattered cases of higher temperatures recorded in the group in which sulfonamide was not used, it does not appear that the degree is great enough to draw any positive conclusions as to the effect of the local use of sulfonamide in reducing the possibility of general sepsis and fever in the immediate postpartum period, all other aspects of aseptic technique in the handling of the deliveries in both series of cases otherwise being equal. It does, however, indicate a very desirable trend if this discrepancy can be maintained to the same degree in subsequent series of cases.

TABLE I. HIGHEST TEMPERATURE OF EACH CASE DURING ENTIRE HOSPITAL STAY

NUMBER OF CASES IN WHICH SULFATHIAZOLE WAS USED	TEMP. ° F.	NUMBER OF CASES IN WHICH NO SULFATHIAZOLE WAS USED
1	98	1
4	98 ²	3
5	98 ⁴	2
22	98 ⁶	43
9	98 ⁸	20
20	99	26
6	99 ²	10
5	99 ⁴	7
2	99 ⁶	6
1	99 ⁸	1
4	100	4
1	100 ²	1
0	100 ⁴	1
0	100 ⁶	0
0	100 ⁸	1
1	101	1
0	101 ⁶	1
0	101 ⁸	1
0	102	1
0	103 ²	2
0	104	1
Total 81		Total 133

The comparison of healing of the perineum of patients treated with 5 Gm. of sulfathiazole powder with those not so treated is given in Tables II and III. Out of 62 cases with episiotomy alone in the sulfonamide series, there were 12 cases, or 19.3 per cent, which developed redness and edema on one or more days. In the control group there were 30 cases, or 40.5 per cent of 74 patients, who had

THE USE OF SULFATHIAZOLE POWDER IN THE VAGINA IMMEDIATELY AFTER COMPLETION OF DELIVERY

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A STUDY of the effect of sulfathiazole powder in the vagina immediately after completion of delivery was begun in 1946. The objective was to evaluate the effect of its use upon the morbidity of the early postpartum period with special reference to healing of episiotomy wounds and vaginal lacerations of various degree, the amount and type of vaginal discharge whether there had been any repair or not, the degree of pain in the perineum, and last, the influence upon the general well-being of the patient.

Preliminary Approach

In the first series of cases which preceded those in which the present method was adopted, the sulfathiazole powder was dusted into the episiotomy wounds and vaginal lacerations before suturing. This was done on alternate cases and the results obtained when compared with the controls showed a satisfactory improvement in most cases, yet there occurred instances where it appeared that delay in wound healing, which others had demonstrated by carefully controlled experiments, was taking place. To overcome this objection, it was felt that perhaps the powdered sulfonamide might be used as a barrier to any wound infection which could take place in the early postoperative period by placing it over the sutured wound instead of into it. When this was done the results were strikingly better than before.

Present Study

The procedure, which was adopted and used without further modification in the next 265 cases as well as in the final series of 214 cases which forms the basis for this study, is very easily performed. After the baby and placenta have been delivered and all the necessary repair completed and bleeding controlled to the satisfaction of the operator, the labia are separated with two fingers and 5 Gm. of sulfathiazole powder is instilled deep into the vaginal tract and spread down into the posterior fornix and about the cervix with the index and middle fingers. This maneuver has the additional advantage of being a final check for any sponge previously overlooked.

The intermediate series of 265 consecutive vaginal deliveries performed by the authors since the institution of this treatment terminated on June 15, 1948. Since this group included all vaginal deliveries, this meant that sulfathiazole powder was used in cases of episiotomy alone, episiotomy with various degrees and numbers of lacerations, lacerations alone, and, finally, those in which no laceration occurred.

The final series which forms the basis of the present comparison includes all vaginal deliveries performed at Glenville Hospital and Booth Memorial Hospital from June 15, 1948, to Aug. 1, 1948. This series consists of two groups: the first in which sulfathiazole powder was used, and the second in which no sulfonamide whatsoever was used in the vagina. The first group consists of all

TABLE III. HEALING OF PERINEUM—5 GM. OF SULFATHIAZOLE POWDER USED IN VAGINA

TYPE OF REPAIR	NUMBER OF CASES SHOWING GOOD HEALING	NUMBER OF PATIENTS DEVELOPING EDEMA AND REDNESS WITH POSTPARTUM DAYS OF OCCURRENCE RECORDED	SEPARATION OF WOUND AND GROSS INFECTION
Episiotomy only 62	50	12 1 on 4th, 5th, and 6th days 2 on 3rd day 3 on 2nd day 4 on 2nd day 5 on 2nd day 6 on 1st and 2nd days 7 on 1st and 2nd days 8 on 3rd day 9 on 3rd day 10 on 1st day 11 on 1st, 2nd, 3rd, and 4th days 12 on 2nd and 3rd days	None
No repair 14	14	None	None
1° laceration only 4	3	1 on 4th day	None
2° laceration only 0	-	-	-
Episiotomy and laceration 1	1	1 on 4th day	-

TABLE IV. AMOUNT AND ODOR OF LOCHIA IN POSTPARTUM PERIOD

	AMOUNT OF LOCHIA			ODOR OF LOCHIA		
	SLIGHT	MODERATE	PROFUSE	NONE	SLIGHT	FOUL
5 Gm. sulfathiazole powder used	11	54	16	35	43	3
No sulfathiazole powder used	15	47	71	15	65	53

TABLE II. HEALING OF PERINEUM—No SULFATHIAZOLE POWDER USED

TYPE OF REPAIR	NUMBER OF CASES SHOWING GOOD HEALING	NUMBER OF PATIENTS DEVELOPING EDEMA AND REDNESS WITH POSTPARTUM DAYS OF OCCURRENCE RECORDED	SEPARATION OF WOUND AND GROSS INFECTION OCCURRED WITH POST- PARTUM DAY RECORDED
Episiotomy only 74	44	30	
		1 on 4th, 5th, and 6th days	
		2 on 4th and 5th days	
		3 on 6th and 7th days	→ Separated 8th day → Went home
		4 on 3rd and 4th days	
		5 on 3rd, 4th, 5th, 6th, and 7th days	
		6 on 3rd, 4th, and 5th days	
		7 on 4th day	
		8 on 4th day	
		9 on 3rd and 4th days	
		10 on 5th day	
		11 on 2nd day	
		12 on 5th day	
		13 on 3rd, 4th, 5th, 6th, and 7th days	
		14 on 3rd and 4th days	
		15 on 2nd, 3rd, 4th, 5th, and 6th days	→ Separated 6th, 7th, and 8th days → Went home
		16 on 5th day	
		17 on 3rd, 4th, 5th, and 6th days	
		18 on 4th day	
		19 on 4th, 5th 6th, and 7th days	
		20 on 5th and 6th days	
		21 on 3rd, 4th, 5th, and 6th days	
		22 on 4th and 5th days	
		23 on 3rd day	
		24 on 4th and 5th day	
		25 on 2nd day	
		26 on 4th day	
		27 on 3rd, 4th, and 5th days	→ Separated 6th, 7th, 8th and 9th days → Went home
		28 on 3rd day	
		29 on 3rd and 4th days	→ Separated 5th, 6th, 7th, 8th and 9th days → Went home
		30 on 2nd, 3rd, 4th, and 5th days	
No repair 48	47	1 on fifth day	
1° laceration only 8	6	1 on 3rd day	
		2 on 3rd, 4th, and 5th days	
2° laceration only 1	0	1 on 3rd and 4th days	
Episiotomy and laceration 2	1	1 on 2nd, 3rd, 4th, and 5th days	

there were 48, or 55.2 per cent, who needed medication for relief. There were two patients with laceration alone in the nonsulfathiazole group who needed medication for pain while none of the sulfonamide group had to have medication for perineal pain. In addition, there were two with episiotomy and laceration in the control group who needed relief for pain whereas there were none in the treated group.

TABLE VI. DEGREE OF PAIN IN PERINEUM

SULFATHIAZOLE USED	NO REPAIR		EPISIOTOMY		LACERATION		EPISIOTOMY AND LACERATION	
	YES	NO	YES	NO	YES	NO	YES	NO
No pain	5	19	5	6	3	5	0	0
Pain but no medication given	4	10	37	33	4	4	3	4
Medication given for pain	0	0	20	48	0	2	0	2

History and Review

The use of local concentration of sulfonamide compounds inserted into wounds by Hawking did not produce necrosis in experimental wounds and only very slight depression of fibroblast formation. This was confirmed by Chambers, Harris, Schumann, and Ferguson. The chief theoretical disadvantage of the use of sulfathiazole is its tendency to clump and form insoluble masses which remain as foreign bodies in the tissues. As compared to sulfanilamide, the drug is much less soluble in water solution or in serum. The relatively low solubility may be an advantage in that the drug persists in situ for a longer period and it may be concluded that probably the optimum combination of high concentration plus sufficient duration is greater with sulfathiazole when compared to sulfanilamide, sulfapyridine, or sulfadiazine. By using sulfathiazole locally in this manner a dual purpose is accomplished. There is suppression of bacterial growth in the ideal culture medium provided by the lochia, as well as the formation of a barrier to the bacteria at the wound entrance during the first critical period when the healing process seals the wound sufficiently to enable complete healing to take place without the complicating factor of infection.

The pathogenic organisms commonly found in the vagina against which sulfathiazole is effective in varying degrees are the beta hemolytic streptococcus, staphylococcus, pneumococcus, gonococcus, colon group, *Proteus vulgaris*, *Clostridium perfringens*, *Clostridium septicum*, *Clostridium oedematiens*, and even in a measure the tetanus bacillus. Those against which it is ineffective are *Bacillus proteus*, most of the *Streptococcus viridans* groups and most viruses. Therefore, it then becomes apparent why the results following its use have been uniformly good, since even in the cases when no gross break in the continuity of the mucosa or skin has occurred there is, nevertheless, tissue susceptibility to infection due to the varying degrees of trauma incident to the compression, abrasion, and stretching of tissues which result during the process of delivery.

Fahraeus showed that instillation of two suppositories each containing 0.5 Gm. of sulfanilamid-thiazole every 12 hours from admission until the fifth puerperal day in 212 primiparas delivered of full-term or premature babies compared very favorable with a control group of 217 of the nontreated patients.

Ackman and Wilson used an emulsion of finely powdered sulfathiazole 5 per cent in a mix of 2 per cent triethanolamine, 24 per cent distilled water, 5 per cent white beeswax, and 64 per cent liquid paraffin impregnated in a pack and placed in the vagina following surgery with very good results.

Manuel found sulfanilamide solution for douche together with sulfonamide internally very efficacious for vaginal infection.

poor healing and, in addition, there were four instances of wound separation as compared to none in the group treated with sulfathiazole. The mode of healing in the patients who had first- or second-degree lacerations only was satisfactory in both series and because of the rather small number of cases in these groups, no other deduction can be made at this time.

One of the most obvious differences in the two groups of cases which was noted very early after this procedure was added to the routine of delivery was the decrease in the amount of lochia and the great decrease in the amount of odor. Whereas medically these factors had no particular significance other than convenience to both patient and nurses, the fact cannot be overlooked that from the esthetic standpoint the very notable decrease in offensive odor of the lochia makes a world of difference to everyone concerned. In Table IV is shown the rather marked difference in the preponderance of cases with profuse discharge in the nonsulfathiazole-treated cases. There were 71 patients out of 133, a percentage of 53.3 per cent, who had a profuse amount of lochia on one or more postpartum days as compared to the treated group which had 16 patients out of 81, or 19.7 per cent. Of those with a slight amount of lochia, there were 15 in the nontreated group, or 11.3 per cent, as against 11 in the other, or 13.6 per cent. In the ones with a moderate amount of discharge, the distribution was 66.7 per cent in the treated and 35.4 per cent in the other. It may be concluded that there was a definite suppression in the amount of lochia in the treated cases. But from the standpoint of nicety and refinement it may be stated that the simplicity of performance and the almost negligible element of time required in the added procedure as well as the minimal expense involved is a small outlay for the marked suppression of the offensive odor of the lochia which is realized. There were only three patients, or 3.7 per cent, who had foul lochia on one or more postpartum days in the treated group as compared to 53 patients, or 39.8 per cent, in the nontreated. Of those with absence of foul odor there were 35 patients, or 43.2 per cent in the treated, as compared to 15 or 11.3 per cent in the nontreated. Those with slightly foul lochia were 53.1 per cent in the treated and 48.9 per cent in the control.

TABLE V. GENERAL CONDITION OF PATIENT

	FAIR	GOOD
Sulfathiazole group	2	79
No sulfathiazole group	19	114

Regarding the general well-being of the patient, it may be noted in Table V that there were only two patients who were considered fairly good as compared to 79 who were good in the treated group, whereas in the nontreated group 19 were fairly good and the remaining 114 were good. It is admitted that by this process of evaluation of the general condition of the patient it is more difficult to arrive at an accurate appraisal in every instance, but the much better showing in the treated group is indicative of the fact that the favorable influence of the other factors, as has been demonstrated, is reflected in the condition of the patient as a whole.

When comparing the amount of pain arising in the perineum alone and for which medication was necessary, the largest series of patients needing relief were found among those who had episiotomies performed upon them. In this category there were 62 patients with episiotomy upon whom sulfathiazole was used. Out of this number, 20, or 32.2 per cent, needed medication on one or more postpartum days for the control of pain as shown in Table VI. Of the 87 cases of episiotomy in which no sulfathiazole powder was instilled into the vagina,

8. The general condition of the patients in the treated group was found to be better than in the control group.

9. The lack of any allergic reactions to the use of sulfathiazole powder as described in this procedure has been noted in a total of 346 cases to date.

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Siegler developed a 10 per cent sulfathiazole in acid-base jelly for the treatment of vaginitis and cervicitis with which response to treatment was excellent whether the vaginitis was trichomonal, monilial, or nonspecific in origin. He reports sixteen failures in which the infection was due primarily to trichomonas and two to monilia.

Similar good results were obtained by Roblee, who used sulfathiazole incorporated in an acid jelly base in treating various types of cervicitis and vaginitis.

Discussion

The use of sulfathiazole powder locally in the vagina immediately following delivery has three advantages over other methods of sulfonamide application previously advocated. In the first place, there is the ready accessibility of the 5-Gm. package of sterile sulfathiazole powder. Second, no special type of applicator is necessary to instill the powder into the vagina. The labia are merely separated with the fingers, the powder poured in and evenly distributed throughout the vagina and about the cervix. Third, it is one operation, quickly accomplished in a few seconds with no further work or procedure necessary.

There is, in addition, the consideration of possible allergic reactions to the use of this drug. Local allergy to the drug was anticipated, but to date no untoward reactions have been noted which might be interpreted in this light. In view of the experience to date, it appears that any unpleasant reactions to the drug will be extremely uncommon if they will occur at all under the conditions of this particular method of use. The blood level of sulfathiazole from absorption through the vaginal mucosa is negligible. It may therefore be assumed that adverse systemic reactions to such use of sulfathiazole may be disregarded altogether. The benefits derived from the use of this procedure in the management of all vaginal deliveries are most welcome, while at the same time no contraindications have appeared which would tend to make its use undesirable.

Summary and Conclusions

1. The prophylactic use of sulfathiazole powder in the vagina as a last step in the performance of vaginal delivery is described.
2. There is a definite suppression in the amount of lochia in the treated cases.
3. There occurs a marked suppression of offensive odor of the lochia in the patients treated by this method.
4. Redness and edema of episiotomy wounds occurred in 19.3 per cent of sulfathiazole-treated patients as compared to 40.5 per cent in the nontreated group.
5. No case of wound disruption has occurred in the series where sulfathiazole was used whereas it occurred four times in the control series.
6. There was a tendency toward lesser temperature elevation in the treated group.
7. Pain, especially in patients who had episiotomies, was severe enough to necessitate medication in 32.2 per cent of the treated group as compared to 55.2 per cent of the nontreated group.

Approximately 22 per cent of the cases occurred before age 30, 62 per cent occurred between ages 30 and 40, while 15 per cent occurred after age 40. This illustrates the fact that carcinoma of the cervix during pregnancy reaches its maximum occurrences during the 30 to 40 age group. The average age of these patients was 33.9 years, the youngest being 18, and the oldest 45 years of age.

Gravidity and Stage of Pregnancy.—In 14, or 11.2 per cent, of the cases, carcinoma occurred in the first pregnancy, giving a ratio of multipara to primipara of approximately 8:1, whereas in normal pregnant patients, the ratio is about 5:3. There was an average of five pregnancies per patient in this series. The greatest number of pregnancies in any one case was 13.

The entire series showed that in the first trimester of pregnancy there were 39 cases, three of which were one month pregnant. During the second trimester, there were only 11 cases, the remaining 73 cases occurring in the last trimester, 59 of whom had full-term pregnancies. One case from the group had carcinoma of the cervix complicated by an ectopic pregnancy. Our five-year survivals with no evidence of disease showed no cases in which the disease was diagnosed in the second trimester. In the first trimester, 22.2 per cent and in the last trimester, 26.5 per cent of the cases survived five years with no evidence of the disease. The cases in this last group were all term pregnancies, while in Maino and Mussey's¹ series of cases there were no cases that had carcinoma of the cervix at term that survived five years. The carcinoma of the cervix coexistent with ectopic pregnancy also survived five years.

Symptoms and Their Duration.—The significant manifestations of carcinoma of the cervix during pregnancy are the usual symptoms of carcinoma of the cervix modified by those of pregnancy. The initial symptoms and also the most common were vaginal bleeding, found in 73 per cent of the cases and abnormal vaginal discharge (purulent, watery, or bloody) in 19 per cent of the cases. The bleeding under these circumstances is characteristically painless and may be profuse or merely spotty. It may be irregular or progressive in amount. Abnormal discharge, which may become watery, purulent, or foul, may be a late symptom, as well as loss of weight, pain, and palpable metastatic extension. Unfortunately, carcinoma of the cervix may be a silent clinical entity with no symptomatology as was seen in eight per cent of our cases, the cancer being discovered during routine examination.

The duration of symptoms was found to be much shorter in this series of cases than in that of a group of cases of carcinoma of the cervix without pregnancy. This may be accounted for by the fact that the patient is more likely to be concerned about her condition during pregnancy than she would be normally. Ironically, many of the patients had symptoms of vaginal bleeding or discharge for periods ranging from one to nine months before the correct diagnosis was made and the patient referred here for treatment. These manifestations are often misinterpreted when the neoplasm is associated with pregnancy because they may represent a threatened abortion or ectopic pregnancy during the first trimester, and placenta praevia, or premature separation of the placenta during the last trimester of pregnancy. But we would like to stress the point that has been brought out innumerable times in the literature that should these symptoms present themselves, the obstetrician or gynecologist, in order to establish a differential diagnosis, should overcome the persistent fear of interrupting the pregnancy by performing a thorough, sterile pelvic examination during any stage of pregnancy and institute the necessary diagnostic procedures to rule out the presence of any coexistent malignancy. Obviously, in this way, carcinoma of the cervix, coincidental with pregnancy, can be detected in its early stages and as a result effective therapy may be employed leading to more favorable results.

CARCINOMA OF THE CERVIX CONCOMITANT WITH PREGNANCY

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CONCOMITANT malignancy of the uterine cervix and pregnancy are considered to be a comparatively rare combination. This is necessarily so when one realizes that the age distribution for pregnancy is declining and is at a low level for the age period when the cervix malignancy age distribution is beginning to increase and that the overlap of the two curves represents a small portion of the entire age distribution of cervix cancer.

Maino and Mussey¹ have reported 0.7 per cent of coexistent cervix malignancy with pregnancy in 3,750 cases of cancer of the cervix. Danforth,² from another point of view, reports that in 10,000 pregnancies there were 0.032 per cent with cervix malignancy.

Although the incidence is comparatively low, it represents a complication which must be born in mind constantly as a possibility when the symptom of painless bleeding is present during pregnancy. This aspect has been emphasized by Strauss,³ Kobak et al.,⁴ Willson,⁵ Maino and Mussey,¹ and others.

Case Material Studied

A review of 4,652 cases of carcinoma of the cervix admitted to this institution during the years 1917 to 1947 shows that 124 or 2.6 per cent were pregnant or had been pregnant within one year preceding admission. The selection of one year preceding admission is arbitrary, but because of the reasons below, it seemed reasonable to conclude that the two conditions were coexistent within that period.

1. The majority of the associated cases were in the far-advanced stages, and corresponded with the stages of the coexistent group.

2. In most instances, the carcinoma was diagnosed as such within a short interval following pregnancy.

3. A review of the case histories revealed the fact that nearly all had symptoms of bleeding or bloody vaginal discharge before, during, and immediately following pregnancy.

We feel that this information indicates almost incontrovertibly that the carcinoma was present before or occurred during pregnancy.

The breakdown of the 124 cases into the status of the two conditions shows that 36 cases were pregnant at the time of admission. In the remaining 88 cases, carcinoma of the cervix was diagnosed during the postpartum period which ranged from two weeks to one year, the majority in less than three months.

Age.—It is a well-known fact that carcinoma of the cervix is essentially a disease of the middle years and its frequency increases rapidly after age 35, reaching a peak at 47 years of age. Sadugor and Palmer⁶ found it to be still relatively common until age 65, after which there was a gradual decrease in the incidence. Pregnancy, on the other hand, decreases rapidly after the age 35. Therefore, in dealing with cases of pregnancy complicated by cancer of the cervix, we find a younger age group of patients and therefore a much lower incidence of these two jointly.

All cervix cases were classified according to the League of Nations recommendations and since it is recommended that all patients who received treatment for their malignancy elsewhere prior to admission here be eliminated, we have excluded 17 patients who fall into this category. Thus, by eliminating the patients treated subsequent to 1942 and those who received treatment prior to admission, the number of pregnancy cases to be compared with the group as a whole has been reduced to 78.

Although we are not comparing two comparable groups because the age distribution is markedly different, yet, because further elimination would still further reduce a comparatively small sample, a preliminary study of the end results of these two groups was made.

The breakdown of the two groups into clinical stages and end results of each stage, as well as the over-all survival is shown in Table I. It can be noted that there is no significant difference in the survival rate of the two groups, either in the individual stages or in the collective survival of 26.9 per cent for Group I and 27.5 per cent for Group II. Fortunately, the distribution of the cases into the various stages of the disease is essentially the same for both groups and the collective survival rates may be compared directly. Had there been a preponderance of the cases in any one stage, the results could not have been compared directly. We have, therefore, tentatively concluded from the preliminary breakdown that insofar as the ultimate cure rate is concerned, pregnancy does not influence the end results.

TABLE I

CARCINOMA OF THE CERVIX ASSOCIATED WITH PREGNANCY, 1917 TO 1942 INCLUSIVE					
	STAGE	NUMBER TREATED	PER CENT OF TOTAL	5-YEAR SURVIVAL NUMBER	FREE OF DISEASE PER CENT
Group I	I	9	11.5	6	66.6
	II	19	24.4	8	42.1
	III	28	35.9	6	21.4
	IV	22	28.2	1	4.5
	Total	78		21	26.9
ALL CERVIX CASES—1917 TO 1942 (INCLUDING PREGNANCIES)					
	STAGE	NUMBER TREATED	PER CENT OF TOTAL	5-YEAR SURVIVAL NUMBER	FREE OF DISEASE PER CENT
Group II	I	304	9.3	198	65.1
	II	833	25.6	375	45.0
	III	1093	33.6	290	26.5
	IV	1021	31.4	32	3.1
	Total	3251		895	27.5

A more rigorous examination of the data required further elimination. The radiation technique had become standardized in 1933; therefore, only the cases admitted from 1933 to 1942 were considered in both groups and since age does influence the end results in carcinoma of the cervix, increased age being associated with increased life expectancy, only those patients were used in Group II who were 45 years of age or younger. Thus, in Table II the five-year end results of two comparable groups of cases, 48 cases of pregnancy and 702 nonpregnant cervix cases from 1933 to 1942 are presented. Here, again, it can be seen that the stage distribution is essentially the same for the two groups and that the survival rate too is essentially the same for the various stages. However, the number of cases in the various stages in Group I are too small for comparison. The over-all figure of 32.9 per cent for Group II and 37.5 per cent for Group I cases

Type of Lesion.—There were 120 cases of squamous carcinoma of the cervix in this series, the remaining four cases were two adenocarcinomas and two adenocanthomas. The latter four cases died of disease or incidental complications in less than five years.

Treatment.—The treatment of cancer at this Institute has been entirely radiological, as is the case with cervical cancer as a whole. Although the technique and dosages have varied considerably during the interval of this report, the general plan has remained more or less constant. We feel that cases diagnosed as carcinoma of the cervix during pregnancy up until viability is certain, should be treated without regard for the fetus, since any appreciable delay might markedly decrease the mother's chances of survival. If the diagnosis has been delayed until viability is probable, we feel that the patient should have cesarean section without hysterectomy and should be started on radiation therapy as soon as her general condition permits (ten days to two weeks).

Usually spontaneous abortion occurs at about the end of the third week of external radiation and usually this interval has been sufficient for the local infection (secondary to the ulceration of the growth) to be markedly reduced, thus keeping postpartum infection to a minimum. Very little radiation fibrosis has occurred during this interval so that serious lacerations are infrequent.

The choice of this plan seems to be substantiated by Heyman,⁷ who shows that when an induced abortion or section (simple or Porro) was used prior to radiation, only 11.1 per cent survived five years with no evidence of disease whereas subsequently, in a group of cases in which radiation was used and the patient was allowed to abort spontaneously, he obtained a 57 per cent five-year cure rate.

Occasionally, with a bulky growth which does not regress sufficiently with external radiation, spontaneous delivery is difficult or impossible and the dead fetus may necessarily have to be delivered by hysterotomy.

We feel that this plan, whereby the uterus remains, allows a more nearly adequate distribution of intracavitary radiation and also fewer post-treatment bladder and rectal complications. This is in agreement with Kobak et al.,⁴ Beck,⁸ Titus,⁹ and McNeil.¹⁰

Our radiation treatment consists of external radiation (x-ray), 400 to 500 r. to one port daily, or 100 to 150 r. to each of four ports daily for a total of approximately 4,000 r. within 45 days. The dosage to the tumor area depends considerably on the size of the patient. Immediately following completion of the external irradiation, intracavitary radium is given in one treatment period, lasting from 50 to 100 hours, depending upon the size of the patient and amount of radiation from the external radiation previously delivered to the tumor area. We attempt to give on the average 8,500 to 9,000 r. combined x-ray and radium "r.," to a point 2 cm. lateral to the cervical canal, of which on the average about 50 per cent of the total is given by each of the two methods of radiation. Under this plan of treatment, approximately 5,000 combined r. is delivered to a point 5 cm. lateral to the cervical canal, which in the average case approximates the junction of the broad ligaments with the lateral pelvic wall.

End Results of Treatment.—In order to determine whether or not the complication of pregnancy influences the cure rate of squamous-cell carcinoma of the cervix, a preliminary survey was made of the end results of the group of patients with pregnancy (designated as Group I) and compared with the end results of another group of patients which comprised all of the cervix cases including the pregnancy cases treated at this institution during the years 1917 to 1942 inclusive (designated as Group II). No patients of either group admitted subsequent to 1942 were included in this survey. This afforded an opportunity to compare end results on a minimum of five-year survival.

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would seem to indicate a better survival in this last consideration. However, when these values were considered statistically, it was found that the two values do not differ significantly and no importance may be attached to this apparent difference.

TABLE II

PREGNANCIES, 1933 TO 1942 INCLUSIVE, AGES 20 TO 45 YEARS					
	STAGE	NUMBER TREATED	PER CENT OF TOTAL	5-YEAR SURVIVAL NUMBER	FREE OF DISEASE PER CENT
Group I	I	6	12.5	4	66.6
	II	17	35.4	8	47.0
	III	18	37.5	5	27.8
	IV	7	14.6	1	14.3
	Total	48		18.0	37.5 \pm 6.98%

NON-PREGNANT CERVIX CASES, 1933 TO 1942 INCLUSIVE, AGES 20 TO 45 YEARS					
	STAGE	NUMBER TREATED	PER CENT OF TOTAL	5-YEAR SURVIVAL NUMBER	FREE OF DISEASE PER CENT
Group II	I	100	14.2	68	68.0
	II	244	34.8	108	44.2
	III	225	32.0	49	21.8
	IV	133	18.9	6	4.5
	Total	702		231	32.9 \pm 1.76%

The 17 pregnancy patients previously excluded because of treatment prior to admission here showed a five-year survival free of disease of 5.9 per cent. Since the prior treatment elsewhere was predominantly surgical and since the survival is considerably less than that in the group treated here radiologically (5.9 per cent as compared with 26.9 per cent), it seems reasonable to conclude that radical surgical interference is not the proper method of treatment, in which we concur with Heyman.⁷

Summary

One hundred twenty-four coexisting and associated cases of carcinoma of the cervix and pregnancy were studied and five-year end results presented.

The results show almost identical cure rate with carcinoma of the cervix unassociated with pregnancy for the same time interval within the comparable age groups.

Our figures and others tend to show definitely better results when conservative treatment is used than when radical surgery is performed prior to irradiation.

The distribution of clinical stages of carcinoma of the cervix associated with pregnancy is almost identical with the nonpregnant cases. This shows that prenatal and postpartal examinations have been neglected and as a result the disease has not been discovered in its early stages. It is recommended that all patients showing any abnormal symptoms during pregnancy should have a thorough vaginal examination, regardless of the stage of pregnancy. All postpartal cases should have repeated examinations after the structures have returned to normal. We believe that such examinations would result in such patients receiving treatment during the early stages of the disease and the cure rate would be definitely improved.

treatment, it was felt that some more satisfactory method of keeping the cervix within the vagina was necessary because it was imperative that this patient tend her child and her home. On October 10, a Smith-Hodge type pessary No. 5 was inserted after returning the uterus to its normal position. This held the organs in place and it was possible for the patient to be up and about at her duties with no discomfort and no restrictions. After one week, she was re-examined and it was again found that the cervix was normally high in the vagina and that its appearance was normal.

On October 18, the estimated "due date," the patient had spontaneous onset of labor, pains beginning at 6 A.M. She was admitted to the hospital at 12:45 P.M. with contractions every fifteen minutes and the cervix dilated two fingerbreadths. Labor progressed slowly because of poorly developed, infrequent contractions. At 4 P.M. pains were occurring every four minutes and were only of moderate severity. At this time vaginal examination was done and it was found that the cervix was dilated $2\frac{1}{2}$ fingerbreadths. The membranes were artificially ruptured. Soon after this the contractions became more frequent and more severe but dilatation still progressed slowly. At 5:45 P.M., 100 mg. of Demerol were given intramuscularly. Dilatation began to be apparent very soon after this, so that at 6:45 it was found to be four fingerbreadths. The pessary was removed at this time. Spontaneous delivery of a female infant weighing 6 pounds, $5\frac{3}{4}$ ounces was accomplished at 7:30 P.M. and the placenta expressed at 7:35 P.M. Total length of labor was 13 hours, 35 minutes. Old bilateral cervical lacerations were freshened and repaired. The pessary was then reinserted. The postpartum course was entirely normal, with no febrile reaction at any time. The patient was discharged on October 26. On November 30, 1946, she reported for her postnatal examination. The pelvic organs were found to be in a normal multiparous condition with the repaired cervical lacerations perfectly healed. At re-examination on January 13, 1947, the pessary was removed and the only abnormal finding was that of a slight cystocele. The uterus could not be brought down by the patient's efforts, and the cervix was normal in appearance. To date, the condition has remained the same.

CASE 2.—Mrs. E. P., 29 years of age, was first seen in this pregnancy on June 5, 1946. Her last menstrual period began on March 21, 1946. One previous pregnancy had been terminated with outlet forceps and episiotomy on Sept. 21, 1942, after fourteen hours of labor. General physical and laboratory examinations at this time were negative, a diagnosis of early pregnancy was made. Gestation progressed in a normal manner until Sept. 15, 1946, when the patient telephoned to state that there was a protrusion from the vagina. She was advised to go to bed but this was of no avail.

On examination it was found that the cervix was protruding some $2\frac{1}{2}$ inches from the vulva and was purplish red, edematous, and oozing blood from its edges. The uterus was returned to its position manually and the cervix returned into the vagina. A Smith-Hodge type pessary No. 5 was inserted and the uterus stayed in place perfectly. The patient experienced no discomfort and immediately was able to be about her business unhampered. Pregnancy progressed normally and the patient went on until Jan. 11, 1947, when it was decided to try induction of labor because of a calculated two-week postmaturity. At the time that induction was begun the cervix was already two fingerbreadths dilated. Induction was instituted by rupture of the membranes and the use of two doses of Calgluquine, 2.5 c.c. each, at one-hour intervals. Two and a half hours after the rupture of the membranes, and one and a quarter hours after the onset of labor, dilatation reached $4\frac{1}{2}$ fingerbreadths and the pessary was removed. Fifteen minutes later, spontaneous delivery of a male infant weighing 9 pounds, $13\frac{3}{4}$ ounces was accomplished with the aid of an episiotomy. The placenta was expelled two minutes after the delivery of the baby. The episiotomy was repaired and the pessary reinserted. The postpartum course was entirely afebrile and without event. The patient was discharged from the hospital on the eighth postpartum day.

On February 22 the patient reported for postnatal examination. The pelvic organs had involuted to the point where all seemed to be in normal condition except for the presence

PROLAPSE OF THE UTERUS AND PREGNANCY*

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PROLAPSE of the uterus and pregnancy are infrequently associated conditions. Only 170 cases were culled from the literature by Kibel¹ in 1944 and a scattered few have been reported since then. The rarity of the coexistence of these two conditions is reflected by the statistics of Kibel, who reports a ratio of 1 to 15,696 deliveries at Bronx Hospital and by Keettel,² who found 1 case in 13,000 deliveries at University Hospital in Iowa City. In most previously reported instances, pregnancy was superimposed upon pre-existing prolapse of varying degree and the condition was obvious early in the pregnancy. We are reporting on four cases of combined prolapse and pregnancy, two of these showing the prolapse relatively late in the gestation. Since the condition under consideration is uncommon and no full agreement as to treatment can be found in the reports of previous authors, we have set out to cite our cases and to suggest a rationale for conservative and successful treatment of this combination of factors.

Case Reports

CASE 1.—Mrs. C. F., aged 31 years, was first seen on May 6, 1946. Her last regular menstrual period was on Jan. 11, 1946, and she had felt well throughout the intervening period. She had had one previous full-term pregnancy that terminated in a sixty-five hour labor with a difficult forceps delivery, three years before. The past history was irrelevant except for an appendectomy in 1933. Physical examination at this time revealed a pregnancy reaching to three fingerbreadths below the umbilicus, a moderately flat pelvis, and an otherwise healthy, albeit thin, individual. Except for a hypotension (98/60), all laboratory tests were within normal limits. Pregnancy progressed uneventfully until Sept. 11, 1946, when the patient called and reported that there had been a sudden appearance of a mass at, and through the vulva. The patient was immediately hospitalized. Examination revealed a purplish blue, edematous, angry-looking mass, 5 cm. in diameter, protruding about three inches outside the vulva. Vaginal examination under sterile precautions was done immediately and the mass felt was determined to be cervix uteri with the uterus itself lowered to the point where the lower uterine segment and the contained fetal head were practically resting on the perineum. The uterus was gently pushed up into the abdomen and the cervix returned to the vagina. The patient was put to bed in a slight Trendelenburg position and during the period of bed rest, a matter of a few days, the condition remained alleviated. Examination of the cervix by means of a vaginal speculum revealed a normal-appearing organ which had lost all of its edema and discoloration. The patient was sent home and told to remain in bed. After one week, with the condition remaining as it was on leaving the hospital, she was allowed out of bed and in a few days the prolapse recurred. After several weeks of in-bed and out-of-bed

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the uterus. In such a situation, the softening and stretching of the pelvic supporting structures associated with a pregnancy would act to aggravate and make more marked any prolapse condition. The supporting structures affected when prolapse exists are the cardinal ligaments, the pubocervical ligaments, the uterosacral ligaments, the fascias of the pelvic floor, the vaginal and perineal tissues, and, perhaps slightly, the round ligaments.

From a purely obstetric viewpoint, prolapse of the uterus may be responsible for several types of difficulty. Sterility may be the result of such a condition because a pool of semen cannot be deposited around a cervix that protrudes from the vaginal introitus and because the prolapsed uterus may fill the vagina and prevent copulation. Abortion may be produced as a result of the trauma and vascular congestion that exist in a prolapsed uterus that contains a pregnancy. Infection can readily result when the protruding highly vascular and easily injured cervix is subjected to trauma over a rather long period of time. Finally, cervical dystocia is commonly associated with prolapsed uterus.

When prolapse of a degree exists before pregnancy takes place, it is to be expected that the condition of uterine descensus will be aggravated by the changes that take place in the tissues as a result of the pregnancy. This condition will remain annoying or incapacitating until such a time as the pregnancy has progressed sufficiently to raise the uterus into the abdomen and pull the cervix up into the vagina. This effects an apparent cure of the prolapse which lasts until the pregnancy is completed. Following this, the pre-existing condition returns, probably to a worse degree than before the pregnancy. This pattern is followed by the majority of patients, but occasionally a prolapse will not be pulled up as the pregnancy progresses and the condition will be evident throughout the gestation. This has necessitated patients being kept in bed for varying lengths of time even up to the entire course of pregnancy. Where prolapse is allowed to exist throughout the pregnancy with just the aid of postural relief, the patient comes to labor with an existing prolapse and the great difficulties reported in the literature may result. It is in such patients and in those in whom the prolapse first became evident in late pregnancy that the severe cervical dystocias occur. Patients 1 and 2 above fall into this category. Not knowing which patients will retain prolapse throughout the pregnancy, and having had such good results in our treatment, we feel that in spite of the time of occurrence of the prolapse, all patients who fall into this group may be treated alike and all will respond well. There is not much question that patients with pre-existing prolapse will need surgical relief after the pregnancy and puerperal involution periods are completed, but in the patient in whom prolapse occurs rather late in pregnancy there is hope that this form of treatment may bring about an alleviation of the prolapsed condition. At any rate, we feel that all patients are relieved during the pregnancy and that the labors of these patients can be made less arduous by the application of our method of treatment.

of a moderate cervical erosion. The patient was re-examined one month later and the pessary was removed. The cervical erosion was treated by cauterization. All of the pelvic organs gave a normal multiparous appearance without even cystocele or rectocele being present. On healing of the erosion the patient was discharged.

CASE 3.—Mrs. J. M., aged 24 years, was first seen on July 16, 1946, with early pregnancy and prolapse of the uterus. Her last period was on April 8, 1946. This was her second pregnancy, her first having terminated Oct. 15, 1944, and the protrusion of the cervix had been present since that time. Physical and laboratory examinations were negative except for the pregnancy and the prolapse. It was felt that when pregnancy had progressed to the point where the uterus was pulled up into the abdomen, the cervix would be pulled up into the vagina and the prolapse cured for the duration of the pregnancy. This did not take place. On October 25 the prolapse was so annoying and the cervix had taken on such a great amount of edema and irritation that the discomfort from it and the appearance of it were alarming. A Smith-Hodge type pessary No. 5 was inserted and the uterus and cervix put into place. This position was maintained with complete comfort and rapid return of the appearance of the cervix to normal. Labor began spontaneously on Jan. 22, 1947, and after dilatation had progressed to four fingerbreadths, sterile vaginal examination was done, the pessary was removed, and the membranes were ruptured. Thirty-five minutes later the patient was delivered, spontaneously, of a female infant weighing 7 pounds, after a five-hour labor. Instead of using the pessary puerperally, a vaginal pack was inserted and removed in twenty-four hours. At the time of her postpartum examination on March 14, 1947, the prolapse still was found to exist and was treated subsequently by surgery.

CASE 4.—Mrs. A. C., 33 years of age, was first seen on April 8, 1947. She had had two previous pregnancies with a prolapse of the uterus dating from the last of these. Her last regular menstrual period had begun on Feb. 1, 1947, and her expected date of delivery was estimated to be about Nov. 8, 1947. A Smith-Hodge type pessary was inserted into the vagina on the first examination and left in place until May 15, 1947, when it was felt that the size of the uterus would act to maintain that organ as an abdominal organ and relieve the prolapse until at least after delivery. The prolapse recurred almost immediately and the patient developed an incarceration of the uterus with an overdistention of the bladder and paradoxical incontinence. After emptying the bladder of 1,000 c.c. of urine, the prolapse was replaced and the pessary reinserted. All discomfort stopped at once and the patient remained comfortable throughout the remainder of the pregnancy.

On Nov. 13, 1947, at 4:30 A.M., labor began. The patient entered the hospital at 6:30 A.M. with pains occurring at five-minute intervals. Sterile vaginal examination was done at 7:50 A.M. and the cervix was found to be completely dilated. The pessary was removed, the membranes were ruptured artificially and the patient delivered spontaneously at 8:08 A.M. The placenta was expressed at 8:09 A.M., a total labor of three hours, thirty-nine minutes. The pessary was reinserted. Except for a moderate postpartum hemorrhage, the puerperal period was entirely comfortable and without event.

The patient reported for postnatal examination on Jan. 12, 1948, at which time the uterus was well held in place, well involuted, and the cervix was found to be clean. The pessary was removed and the uterus showed no tendency to prolapse. In a subsequent telephone report the patient stated that the cervix had descended somewhat but did not protrude from the vulva.

Discussion

Prolapse of the uterus is most commonly seen in women who have had pregnancies and deliveries which had been more or less responsible for the descensus. In order for prolapse to take place, there must be relaxation and tearing down of the structures which are charged with the task of supporting

intervals, until the patient is in labor. When labor has begun to progress, effacement has taken place, and dilatation has proceeded to the point where 6 to 7 cm. of opening has been accomplished, the pessary is removed under sterile vaginal examination precautions. The pessary is cleansed and placed in cold sterilization for subsequent use. Labor has now progressed to the point where the danger of soft-tissue dystocia from the cervix no longer exists because retraction has taken place and the small amount of dilatation necessary to reach completion is easily and quickly accomplished.

When labor is completed and all lacerations and incisions are repaired, the pessary is removed from the sterilizing solution and reinserted. We consider this part of the procedure the most important one and the most radical departure from previously described techniques. It is to this part of the treatment that we ascribe our successful outcomes in Cases 1 and 2 where there were no prolapse conditions present after the involution periods were completed. The success of this therapeutic agent is obtained because the pessary keeps the uterus in proper position for adequate drainage and encourages proper uterine involution. The postpartum use of the pessary also takes the strain off the pelvic supporting structures and allows involution of these structures to take place to as great an extent as is possible. Anticipating questions of introduction of infection by the use of the pessary during pregnancy and in the puerperal period we can only say we have seen no such infection, we can see no reason to expect such infection, and we have no fear of infection.

Conclusions

1. Pregnancy superimposed on prolapse of the uterus and prolapse of the uterus occurring during pregnancy are uncommon combinations of conditions for which no previous adequate standardized treatment has been recommended.
2. Four cases of prolapse of the uterus and pregnancy are presented.
3. Treatment of this combination of conditions by use of a vaginal pessary during pregnancy, the first two-thirds of the first stage of labor and the puerperium is recommended.
4. This treatment has proved successful and presents no contraindications.

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30 NORTH MICHIGAN AVENUE

Discussion

DR. LESTER E. FRANKENTHAL.—I would like to take issue with the essayists as far as their four case reports are concerned. In Case 1, three months post partum there was no evidence of prolapse of either the cervix or the uterus. Case 2 falls into the same category. Case 3 showed evidence of prolapse post partum and was corrected by means of some surgical procedure. Case 4 presented an incarcerated retroverted uterus during pregnancy. However, puerperally, if I remember correctly, there was no evidence of prolapse. Therefore, I feel that three out of the four are not true cases of prolapse of the uterus. They fall into the category of hypertrophied, edematous, elongated cervixes, a condition which is not infrequently seen during pregnancy and labor in the multipara.

In previously reported cases, treatments have varied from the early suggestion of Findley³ that therapeutic abortion and vaginal plastic be employed, to the idea propounded by Keettel² that the patient be delivered by means of Dührssen's incision and forceps or even further to the treatment by Porro cesarean section recommended by Harris.⁴ The standard textbooks of obstetrics make no better suggestions, since Stander⁵ recommends cervical incisions for dystocia and therapeutic abortion for incarcerated prolapsed pregnant uterus. In the group of 170 patients reviewed by Kibel,¹ the entire gamut of treatments were employed (Table I). In this group, the maternal mortality was 6.3 per cent, while the infant mortality was 22.1 per cent. Such statistics are very alarming but can be understood when one considers the picture that a pregnant prolapsed cervix presents. The organ is elongated, edematous, purplish red in color, and is friable and bleeds very readily on touch. Because of this, infection can take place rather easily and adding to such a situation an operative delivery would greatly increase the chances for sepsis. Stander reports such cases of maternal death from infection, and the deaths reported by Kibel were mostly the result of puerperal sepsis. Therefore, it would seem to us, any form of treatment that allows for spontaneous delivery is to be desired over any operative form of delivery.

TABLE I. METHOD OF DELIVERY IN 170 CASES OF PROLAPSE AND PREGNANCY REVIEWED BY KIBEL

METHOD	PER CENT
Spontaneous	34.7
Forceps	23.1
Dührssen's incisions	29.3
Version and extraction	4.3
Craniotomy	7.8
Porro-cesarean	0.8
	100.0

Treatment

As soon as the prolapse becomes evident, or as soon as a patient with prolapse becomes pregnant, the uterus is returned to normal position manually, and a Smith-Hodge type pessary of the proper size is inserted. This supports the uterus in the pelvis, prevents it from descending and, for the period of its use, ostensibly cures the prolapse. With the uterus held in place by the pessary, the patient may be up and about her usual business with no discomfort and without the dangers that might face her with the cervix protruding from the introitus. The use of the pessary in pregnancy is by no means a new procedure, but, in the past, as soon as a patient with a prolapsed pregnant uterus had uterine growth sufficient to pull the uterus into the abdomen and the cervix up into the vagina, the pessary was removed. If the prolapse again became evident, the patient was put to bed and kept there for the duration of the pregnancy because the bogey of obstetrics taught that a foreign body (pessary) in the vagina as term approached was a very dangerous thing. So, even though obstetricians may be advocates of early ambulation post partum, they will keep an otherwise healthy pregnant woman in bed throughout months of her pregnancy because of a simple prolapse which can be easily controlled. We do not remove the pessary, except for cleansing at regular

is a remarkable structure. Many years ago Dr. DeLee and I each had almost duplicate cases of unusual hypertrophy of the cervix in nonpregnant uteri. We amputated the cervix in each case, but in a few years the cervices were again markedly hypertrophied.

In the only two cases of hypertrophy and prolapse of the cervix of a pregnant uterus I have seen, I had no trouble in delivering the patients. I see no objection to the use of a vaginal pessary during pregnancy.

Some of the statistics quoted by the authors are rather old and the prognosis for cases of prolapse of the cervix was poor. In the present state of our knowledge, infection is less important as a hazard than it was in former years.

DR. KLAWANS (Closing).—Dr. Frankenthal it seemed to me misunderstood or misquoted the paper. He apparently feels that unless he or some one close to him examines the patient the prolapse is not recognized. I think the doctors who examined these patients were able to differentiate. My understanding is that in practically every real case of descensus there is an elongated cervix, but when I stated in the paper that the cervix protruded three inches and that the lower uterine segment was lying on the perineum, that I should think would constitute a prolapse. Dr. Frankenthal did not read my statement that I did not expect a result in patients who had previous prolapse. Those patients would probably need surgery but we would save them trouble during labor and discomforts during pregnancy. Dr. Frankenthal stressed tearing of the supporting ligaments, I mentioned no such thing. I quote from the paper: "The postpartum use of the pessary also takes the strain off the pelvic supporting structures and allows involution of these structures to take place." I did not say they went back to normal. Dr. Frankenthal misquoted that. In his statistics from Michael Reese Hospital and from the Maternity Center there is no mention made of when in pregnancy these prolapses were seen, nor was mention made as to whether there was any treatment given. There is no differentiation between prolapses or elongated and hypertrophied cervices. We reserve the privilege of thinking that these patients we reported had true uterine prolapse.

To Dr. Greenhill, the last paper that I reviewed in which Dührssen's incision was advocated to facilitate delivery was written in 1941. That was relatively recent enough to be considered as modern.

Second, the essayists state that the descensus is aggravated by pregnancy. I fail to see where they have adequate proof of this conclusion. At approximately the fourth month of pregnancy the size of the corpus holds the uterus up out of the pelvis and unless there is an edematous cervix there will be no difficulty. As far as the use of a pessary post partum is concerned, the essayists claim that by the use of the pessary the uterus is kept in the proper position, allowing free and adequate drainage from the uterine cavity and likewise allowing the torn vaginal structures to regain their normal tonus. As far as the first part is concerned, I am heartily in accord. As far as the second part is concerned, if the cardinal ligaments, the pubocervical fascia, and the parametrium have been torn by a previous pregnancy, I fail to see how keeping the uterus in an anteverted position is going to allow restoration of these lacerated structures. If such were the case, I should think that the logical conclusion would be that if we had a first- or second-degree prolapse the introduction of a pessary, holding the uterus in the proper position for a period of a few months would suffice to correct the prolapse and removal of the pessary would find a normal genital status. Such is not the case.

From a statistical standpoint I would like to quote some statistics from Michael Reese Maternity Hospital. From Jan. 1, 1942, to date there were approximately 18,000 women delivered. During this time we have had three patients in whom the cervix protruded through the vulvar orifice. In two of these cases, postpartum check-up showed the genital tract to be normal; in other words, the edema and hypertrophy of the cervix had disappeared and there was no longer any problem. In one case, there was still a prolapse and this was treated by a Manchester operation. At the Maternity Center since July 1, 1932, there have been approximately 35,000 deliveries, of which 29,500, or 83 per cent were multiparas. In this number there were 11 women whose cervices protruded through the vulvar orifice; in other words, an incidence of one in 3,200 in the total series or 1 in 2,700 in multiparas.

As far as the treatment of labor is concerned, I do not feel that it requires any special comment. All of these patients had essentially normal deliveries. At Michael Reese Hospital, with the exception of one, all were normal spontaneous vaginal deliveries without complications in the puerperium. One case at the Maternity Center was terminated by means of version and extraction. In none of these cases was there any dystocia due to the edematous cervix or descent of the cervix.

DR. EDWARD L. CORNELL.—I want to warn the younger men not to be too critical of the practicing physician on the question of protrusion of the cervix or elongation of the cervix without protrusion. The practicing physician is not necessarily at fault. I have seen one case occurring in a primipara who came to me about the second month of pregnancy with a beginning prolapse or elongation of the cervix, whichever you wish to call it. The condition gradually became worse. A pessary was used and finally removed when the patient was about five months pregnant and the uterus remained up. It was a relatively easy delivery. She became pregnant again and approximately the same procedure was followed in the second pregnancy. In the interval between the two pregnancies the patient had no prolapse and no evidence of prolapse and no pessary was used post partum. She was allowed to stay in bed twelve or fifteen days, allowed up, and at the postpartum examination we found some descensus but nothing outside the vagina. I have never seen four multiparas with descensus but I am sure that such cases must occur. They can occur with and without the assistance of the physician.

DR. J. P. GREENIILL.—The matter of definition is important. Dr. Frankenthal is correct when he insists we should differentiate between a cervix which is outside the vulva and a real prolapse of the entire uterus. I fully agree that no matter what degree of prolapse there is, in nearly all cases, if pregnancy occurs, the uterus grows up out of the pelvic cavity into the abdomen, but the cervix may protrude out of the vagina. I have never seen a prolapse of the entire uterus which contained a pregnancy outside of the vulva. This condition is a true case of a prolapsed, pregnant uterus. In most cases where the cervix is at or outside the vulva, we are dealing with hypertrophied cervix and not a true prolapse. The cervix

TABLE I. UNSUSPECTED CERVICAL CARCINOMAS DISCOVERED AFTER OPERATION

CASE	YEAR	AGE	PREOPERATIVE DIAGNOSIS	OPERATION	CERVICAL CANCER	TREATMENT	REMARKS	FOLLOW-UP
1	1925	33	Myoma, retroversion, chronic cervicitis	D. & C., myomectomy, left salpingo-oophorectomy, suspension, trachelor- rhaphy, colporrhaphy, appendectomy	Early	Radium, x-ray	No biopsy	Recurrence after 19½ years
2	1926	40	Lacerated and eroded cervix, vaginal re- laxation, retrover- sion subinvolution	D. & C., cauterization, tracheloplasty, colpor- rhaphy, suspension, appendectomy	Grade 3	Hysterectomy, bilateral salpingo- oophorectomy, radium, x-ray	No biopsy	Well 2½ years
3	1928	40	Cystoectocoele, prolapse	D. & C., trachelorrhaphy, colporrhaphy, inter- position operation	Grade 2	X-ray, radium	Carcinoma con- cealed in canal	Well 12 years
4	1928	48	Cystoectocoele, chronic cervicitis, retroversion	D. & C., trachelorrhaphy, colporrhaphy, inter- position operation	Early	Radium, x-ray	No biopsy	Well 11 years
5	1930	56	Cystoectocoele, prolapse	D. & C., trachelorrhaphy, colporrhaphy, suspen- sion, right oophorectomy	Grade 1	Radium, x-ray	No biopsy	Well 14 years
6	1935	39	Adenomyosis, chronic cervicitis, metror- rhagia	D. & C., trachelorrhaphy, subtotal hysterectomy, bilateral salpingo- oophorectomy	Grade 3	Radium, x-ray	Carcinoma missed in preoperative curettings	Died 1½ years

UNSUSPECTED CERVICAL CANCER IN GYNECOLOGICAL PATIENTS

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FEW experiences are more embarrassing to a gynecologist than the receipt of an unexpected pathological report of cervical carcinoma following operation for another condition. Such an occurrence, unfortunately, is not rare.

Bowers (1940), Diddle (1942), Graffagnino and McFetridge (1946), and Munnell (1947) have reported several cases in which carcinoma of the cervix was discovered for the first time by the pathologist after total hysterectomy. Three clinically unsuspected cases of cervical cancer in which the tumor was found incidental to plastic operations were recorded recently by Rubin (1945). Thirty-four per cent of the carcinomas of the cervical stump at the Sloane Hospital were discovered within 2 years following subtotal hysterectomy (Knight, 1943); and von Graff (1934), in a review of 581 published cases of stump cancer, found that symptoms of the tumor appeared within a year of operation in 23.5 per cent. In view of the slow growth of cervical carcinoma in its early stages, it is practically certain that most of these tumors were present but unsuspected at the original operation. Given (1947) observed that one-fourth of the stump cancers at the New York Hospital were discovered immediately after subtotal hysterectomy.

At the Roosevelt Hospital, carcinoma of the cervix has been diagnosed in fourteen cases in which there is no recorded preoperative suspicion of such a tumor. This represents a little over 2 per cent of all the cervical cancers. In most instances, the original operation was probably ill advised and would not have been done had the diagnosis been made beforehand. The recorded descriptions of the cervix suggest that in almost all the cases the tumor could have been detected by biopsy prior to operation. It is the purpose of this report to analyze these fourteen cases, to point out the diagnostic oversights, and to suggest methods for preventing their repetition.

The main features of each case are summarized in Table I. The patients varied in age from 30 to 58 years, the range in which most cervical cancers occur. In patients of this age group, the slightest indication of a cervical abnormality should arouse a suspicion of carcinoma and require that it be ruled out. In five cases, the cervical lesion was discovered in the routine examination of total hysterectomy specimens. Four of these operations were done for myomas, one for adenomyosis. In eight instances, the tumor was found in tissue removed incidental to plastic operations. Seven of these included trachelorrhaphies and one was a combined colporrhaphy preceded by routine curettage, the cervical tumor being discovered in the curettings. In one case, the cervical lesion was revealed in a postoperative biopsy after subtotal hysterectomy for fibroids.

Among the patients who underwent trachelorrhaphy, three also had abdominal uterine suspensions at the same operation, one including a myomectomy

and salpingo-oophorectomy in addition. In two other cases, Watkins interposition operations were done. When the hysterectomy cases were reviewed, it seemed clear that at least three of the operations were performed for symptoms probably related to the unsuspected cervical cancer rather than to the recorded indication. Perhaps the most significant observation in this study is that in only one case was preoperative biopsy of the cervix done.

The choice of operations by which these patients were treated originally is beyond the scope of the present discussion. It should be noted, however, that the cases date back over more than two decades, during which time fashions in gynecological procedures have undergone change. For example, the combination of tracheloplasty and subtotal hysterectomy, once in common vogue, has been replaced largely by total hysterectomy. To an even greater extent, perhaps, have interposition operations been superseded by vaginal hysterectomy and the Manchester-Fothergill procedure.

The following 4 cases have been selected for individual analysis in the hope that the errors they embody may be of value to others.

CASE 2.—A 40-year-old white woman with two children was referred to the hospital for gynoplastic operation three months after the birth of her last child. Her last menstrual period had begun six days prior to admission and lasted two days. The recorded examination described the perineum as relaxed; the cervix soft, eroded, and bleeding slightly, with a large tear in the anterior lip and several smaller tears in the posterior lip; the fundus retroverted, enlarged, and softened. The preoperative diagnosis was laceration and erosion of cervix, cystocele, rectocele, lacerated perineum, retroversion and subinvolution of uterus. Operation the day after admission consisted of dilatation and curettage, anterior and posterior colporrhaphy, trachelorrhaphy, cauterization of cervix, round ligament suspension of uterus (Simpson), and appendectomy. In the process of curettage, the posterior wall of the uterus was accidentally perforated. Pathological report on the excised cervical tissue was epidermoid carcinoma. Twelve days later total hysterectomy and bilateral salpingo-oophorectomy were performed. The patient was given postoperative irradiation and was well two and one-half years later, when she was last seen.

Comment.—This patient's cervix received inadequate preoperative attention, in the mistaken belief that all the pathological alterations in it were the result of recent parturition.

CASE 9.—A 36-year-old Negro woman with two children complained of postmenstrual pain in the right lower quadrant of the abdomen. For the past three months she had noticed slight bleeding after coitus and a thin bloody vaginal discharge several days after each menstrual period. Her cervix was lacerated, eroded, and cystic, and bled easily on touch. The fundus was retroverted and contained a small nodule on its posterior surface. Operation consisted of trachelorrhaphy followed by subtotal abdominal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy. At laparotomy, small myomas and chronic salpingitis were found. Pathological report on the excised cervical tissue was epidermoid carcinoma, plexiform type, grade 2. Postoperatively, the patient received a course of deep x-ray therapy to the pelvis followed by two applications of radium to the cervical stump for a total dose of 2,125 mg. hr. Seven years later she was well with no evidence of tumor recurrence.

Comment.—Preoperative biopsy of the cervix was indicated in this case by the history of postcoital bleeding, metrorrhagia, and the recorded description of the cervix.

CASE 11.—A 41-year-old nullipara began to have profuse, frequent, and irregular menstrual flow, often with clots and cramps, a year and a half before admission. She complained also of a heavy feeling in her pelvis. Her uterus was irregularly enlarged to the level of the umbilicus. The cervix was described as large, round, and smooth. Total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were performed. On pathological examination, in addition to a fibroid uterus, an irregular area of reddish discoloration and surface erosion measuring 7 mm. in diameter was described at the external cervical os. Microscopically, this

7	1936	44	Myomas	Subtotal hysterectomy	Grade 3	Radium, x-ray	Cervix biopsied postoperatively	-----
8	1939	39	Myomas, chronic cervicitis, metrorrhagia	Hysterectomy, bilateral salpingo-oophorectomy	Grade 1	X-ray	No biopsy	Well 1½ years
9	1939	36	Myomas, laceration cervix, chronic cervicitis, metrorrhagia	Trachelorrhaphy, subtotal hysterectomy, bilateral salpingo-oophorectomy, appendectomy	Grade 2	X-ray, radium	No biopsy	Well 7 years
10	1939	30	Lacerated cervix, chronic cervicitis, metrorrhagia	D. & C., trachelorrhaphy, Manchester operation	Grade 2	X-ray, radium	No biopsy	-----
11	1942	41	Myomas, menometrorrhagia	Hysterectomy, bilateral salpingo-oophorectomy, appendectomy	"Car-cinoma in situ"	None	No biopsy	Died of stomach carcinoma 4½ years later
12	1944	50	Myomas, chronic cervicitis, metrorrhagia	Hysterectomy, bilateral salpingo-oophorectomy	Grade 3	X-ray	No biopsy	Well 2½ years
13	1946	44	Cystoectocoele, chronic cervicitis, prolapse	Trachelorrhaphy, colporrhaphy	Very early	Radical hysterectomy, bilateral salpingo-oophorectomy	Carcinoma missed in biopsy	Well 1 year
14	1947	58	Cystoecole, cystitis, prolapse	D. & C., colporrhaphy, Manchester operation	Grade 2	Radium	History misleading carcinoma in canal	-----

on the cervix. In these cases treatment of the cancer has been compromised, either necessitating another laparotomy or making radiation therapy more difficult, more hazardous, and less effective. A more rational method of approach to diseased cervixes would seem to lie in preoperative biopsy before proceeding with major surgical treatment.

That the end results of treatment in this series of cases had not been consistently jeopardized, however, is suggested by the fact that at least five of the fourteen patients remained well for more than five years, and in only two cases was recurrence of the cervical tumor observed. This compares satisfactorily with the good prognosis usually associated with early cervical cancer.

Summary

1. Fourteen cases of unsuspected cervical carcinoma are reported which were discovered postoperatively by routine pathological examination or postoperative biopsy. Approximately 2 per cent of all cervical cancers were discovered in this manner.

2. Meticulous examination of the cervix with biopsy of suspect areas should precede all major gynecological operations.

3. Because of the occasional unsuspected endocervical and endometrial cancer which it brings to light, routine curettage is a worth-while preliminary to vaginal plastic operations.

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Addendum

Since this paper was written, publications by the following authors have mentioned several additional cases in which cervical cancer was discovered for the first time following major gynecological operations for unrelated conditions:

- Diddle, A. W., and Bennett, T. R.: AM. J. OBST. & GYNEC. 55: 669-674, 1948.
Johnson, W. O.: AM. J. OBST. & GYNEC. 56: 100-109, 1948.
Brady, L.: AM. J. OBST. & GYNEC. 56: 939-943, 1948.

was diagnosed as "carcinoma in situ." The patient remained well until almost four years and five months later, when she was readmitted because of abdominal pain of three months' duration. At operation she was found to have generalized abdominal carcinomatosis with ascites, but biopsy of a mesenteric implant was inadequate to establish the primary site of the tumor. The patient died twelve days later, autopsy disclosing an adenocarcinoma of the stomach with rupture and peritonitis. Careful examination of the pelvis failed to reveal any evidence of residual cervical cancer. The pelvic lymph nodes were free of tumor.

Comment.—Although it had no bearing on the ultimate outcome of the case, this patient's cervical lesion might have been discovered by more careful preoperative examination and biopsy.

CASE 14.—A 58-year-old white woman whose menopause had occurred 6 years previously complained of urinary frequency and recurrent attacks of "bleeding from the bladder" during the past year. She was believed to be suffering from hemorrhagic cystitis, and since a moderate cystocele and rectocele were present operative correction was decided upon, in the hope that this might help cure the urinary condition. The cervix was slightly prolapsed in the vagina but the mucosa appeared normal. The fundus and adnexa were atrophic. The urine contained many bacteria and a few leucocytes but no red blood cells. Operation consisted of dilatation and curettage, anterior and posterior colporrhaphy, and a modified Manchester procedure. The curettings, which amounted to only a few tiny fragments, showed epidermoid carcinoma of the cervix, grade 2. Five days postoperatively a 50 mg. capsule of radium was inserted into the cervical canal for sixty hours. Great difficulty was experienced in obtaining adequate exposure, and finally a considerable part of the plastic repair had to be undone before the radium could be inserted.

Comment.—This patient gave a misleading history. Her bleeding, which she later admitted to be from the vagina, resulted from an unsuspected and invisible endocervical carcinoma. Tumors in this location usually can be detected by curettage. The occasional discovery of unsuspected cervical carcinomas and asymptomatic endometrial neoplasms by the simple expedient of curettage recommends this procedure as a routine preliminary to all vaginal plastic operations in which the uterus is to be retained.

Discussion

The brightest prospect for improving the results in the treatment of cervical carcinoma lies in the early detection of cases. Early cervical cancers are discovered in proportion to the frequency with which they are suspected and the diligence with which they are sought. Schiller (1933) reported a 50 per cent reduction in the incidence of undiagnosed carcinoma by meticulous examination of the cervix preoperatively. In several clinics vaginal smears are now used routinely for this purpose, and in a few others all cervixes are biopsied prior to major gynecological operations. Cervical biopsy is so simple and innocuous a procedure that it should be extended to every woman in whom there is the slightest suspicion of a cervical abnormality. A hundred negative biopsies are a small price for the discovery of a single early cervical cancer. It is the early, least suspected cases that are the most readily cured.

It has been common practice in the past, in this and other clinics, to treat various types of pathological cervixes by tracheloplastic operation, doing any necessary vaginal plastic work at the same time. If the excised cervical tissue revealed carcinoma, as it did in seven cases in the present series, further treatment in the form of hysterectomy or irradiation was given. But in a few instances subtotal hysterectomy, uterine suspensions, or interposition operations were also done at the original sitting, without benefit of the pathological report

*When additional sections of the cervix were cut later a distinct area of invasion was found.

sac, umbilicus, and perineum were rejected as not constituting per se an indication for laparotomy, and, therefore, not bearing upon the question of conservative versus radical surgery. This report is concerned with the remaining 138 cases of intra-abdominal, pelvic endometriosis, diagnosed grossly and histologically, and treated by laparotomy at which the childbearing function was anatomically preserved.

Results

TABLE II. RELIEF OF SYMPTOMS

	NUMBER OF CASES	PER CENT
Relieved	68	49.3
Partially relieved	29	21.0
Failure	41	29.7

In Table II, the group of cases classed as "relieved" includes those patients who stated without question that they were relieved, together with those who were "improved" or "better," except for symptoms which were felt to be mild, and in whom pelvic examination was essentially negative. The group classed as "partially relieved" includes those who were, for the most part, helped by operation, but in whom a significant degree of symptoms remained or recurred. If there was any doubt as to a reasonably high degree of symptomatic relief, the case was classed as "partially relieved," rather than "relieved." No further treatment was given in the above two groups. The group classed as "failure" were those in whom continuance or recurrence of symptoms necessitated either radical surgery or radiation therapy.

Pregnancy Following Operation

One hundred twelve patients in the series were married and under 40 years of age; of these, 30, or 26.8 per cent, delivered a total of 39 living children. Twenty-three patients had one child each, six had two children, and one had four children. In addition to the above 30 patients, seven patients reported one miscarriage each. The time between operation and delivery ranged from 11 months to 6 years, the average interval being 2.7 years. Of the above thirty patients who had children, twenty-two were classed as being relieved of their symptoms, three as partially relieved, and five as failures.

The question, "Have you wanted to have children since operation?" was included in the questionnaire letter. While the answers to this question were too few to determine how many of the series as a whole wanted children, there were an appreciable number of answers in the negative. Thus it is possible that there were more potential children in the series than those recorded.

Later Treatment

Forty-one patients, or 29.7 per cent (those classed as "failure" in Table II), required further treatment; this is summarized in Table III.

TABLE III. LATER TREATMENT

Hysterectomy	26
Pelvic laparotomy (miscellaneous procedures)	5
Radium	4
X-ray	6

Pathologic diagnosis is available in twenty of the cases treated by hysterectomy; of these, only nine showed recurrent endometriosis. The findings in the remaining eleven cases include adhesions, chronic salpingitis and oophoritis,

RESULTS IN 138 CASES OF ENDOMETRIOSIS TREATED BY CONSERVATIVE SURGERY

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Harvard Medical School)

IN ENDOMETRIOSIS of sufficient degree to warrant laparotomy, a major problem is whether or not to conserve menstrual function and childbearing ability. While this must be decided for each patient as an individual by the sum of all the factors bearing upon her particular case, it was felt that an evaluation of two questions might be of assistance to the surgeon in this problem. If a conservative operation is performed, first, what are the chances for relief of symptoms or for progression or recurrence of the disease demanding later radical surgery or radiation; and, second, what is the outlook for future pregnancy? Table I, obtained from a review of the literature, summarizes the results of surgery in which the childbearing function was preserved.

TABLE I. RESULTS FROM THE LITERATURE

AUTHOR	YEAR	NO. OF CASES	(EXPRESSED IN PER CENT)			NO. MAR- RIED AND UNDER 40	NO. HAD CHILDREN
			CURED	IM- PROVED	FAIL- URE		
Wharton ¹	1929	4	75		25	4	3
Read and Rogues ²	1929	21	71.5	19.2	9.3		
Smith ³	1929	40		32.5	0	?	2 per cent pregnant
Keene and Kimbrough ⁴	1930	21	95.3	4.7	0	14	28 per cent nor- mal pregnant
Cattell and Swinton ⁵	1936	21	90	10	0	?	3
Pemberton ⁶	1937	107			29	76	15
Counseller ⁷	1938	98	56.2	19.8	24.0	55	6
Payne ⁸	1940	{48	67	26	7	?	21
		25	72	20	8	?	12
Fallas and Rosenblum ⁹	1940	34	58.8	35.3	5.9	?	1 known child
Dannreuther ¹⁰	1941	18	88.8	11.2	0	14	2
Holmes ¹¹	1942	24	29.1	54.1	16.6	?	12.6 per cent
Beecham ¹²	1946	32			6.25	?	2 children 1 "preg. now"

Material

Two hundred fourteen cases of endometriosis treated by conservative surgery in the Free Hospital for Women and its private wing, the Parkway Hospital, from 1905 to 1941 inclusive, are reviewed. The data obtained from the hospital records were supplemented by answers to a questionnaire letter. Fifty-seven cases were rejected because of insufficient follow-up studies. An additional 19 cases, including endometriosis of the cervix, vagina, abdominal scar, hernial

It was felt that evaluation of the degree or severity of symptoms from written records would be invalid. Therefore Table V expresses only the comparative frequency with which each symptom occurred in each of the three above groups. It is seen that these symptoms appear in each group with the same relative frequency. Therefore, no prognosis of value can be derived from this study of symptomatology.

Pathologic Findings.—The pathologic findings in the series are classified as to location of endometriosis on the basis of (a) ovarian endometriosis (i.e., whether it is absent, unilateral, or bilateral) and (b) the presence or absence of the disease elsewhere in the pelvis. This divides the series into the five classes which are listed in the first column of Table VI. The operations by which these five classes were treated are also recorded. Thus, the location and extent of endometriosis are judged both by the operative findings and the magnitude of the operation necessary to relieve them. It is seen that the extent of the disease, and that of the corresponding operation, increases progressively from Class 1 to Class 5. This classification is made in an attempt to determine whether any significant difference in postoperative results exists between the cases with minimal endometriosis and a minor operative procedure at one extreme, and those with a considerable amount of the disease and a comparatively extensive operation at the other.

TABLE VI. PATHOLOGIC FINDINGS CORRELATED WITH SYMPTOMATIC RELIEF AND SUBSEQUENT PREGNANCY

LOCATION OF ENDOMETRIOSIS	OPERATION	NO. OF CASES	SYMPTOMATIC RELIEF (EXPRESSED IN PER CENT)			SUBSEQUENT PREGNANCY	
			RE- LIEVED	PAR- TIAL- LY RE- LIEVED	FAIL- URE	NO. OF CASES MAR- RIED AND OVER 40	PER CENT HAVING CHIL- DREN
1 Negative ovaries Pelvic E.*	Excision of E.	32	59.4	6.2	34.4	26	23.1
2 Unilateral ovarian E. negative pelvis	Resection ovary; or O* or SO*	61	41.0	29.5	29.5	49	24.5
3 Unilateral ovarian E. plus pelvic E.	Resection ovary and excision E.; or O or SO, and excis- ion E.	22	63.6	13.6	22.8	19	36.8
4 Bilateral ovarian E. negative pelvis	Resection both ovaries; or O or SO, and resection other ovary	11	36.3	18.2	45.5	8	25.0
5 Bilateral ovarian E. plus pelvic E.	Resection both ovaries and excis- ion E.; or O or SO, resection other ovary and excision of E.	12	50.0	33.3	16.7	10	30.0
Results in Series as a whole		138	49.3	21.0	29.7	112	26.8

*E - Endometriosis

O - Oophorectomy.

SO - Salpingo-oophorectomy.

Pelvic endometriosis includes involvement of the uterine serosa and supporting ligaments, anterior and posterior cul-de-sac, and elsewhere on the pelvic peritoneum. In the majority of cases it is believed to be slight or moderate, in that many cases show only a few minute implants or a small area with adhesions separated without difficulty. This is particularly true of pelvic endometriosis

retention cysts and fibroids (one case), but no endometriosis was demonstrable. These eleven cases, although symptomatically demanding reoperation, bear out the fact, at least from a pathologic standpoint, that the disease is not always progressive, which is a point in favor of conservatism. The time between the first and second operation ranged between 4 months and 14 years, the average interval being 4.8 years.

Correlations

An attempt is made in this review to ascertain whether any factors exist which might have a bearing upon the postoperative outcome of a case in respect to symptomatic relief and future pregnancy. In other words, are there any criteria that might enable the surgeon to determine which patients are more likely to be symptomatically relieved and become pregnant, after a conservative operation, and which cases are less likely to attain this desired result.

The factors which should be considered in regard to their possible bearing upon this result are age, symptomatology, and pathologic findings.

Age.—The age at the time of operation of the married patients in the series, and of the patients who subsequently delivered children, is given in Table IV.

TABLE IV. AGE INCIDENCE

YEARS (INCLUSIVE)	MARRIED PATIENTS	PATIENTS DELIVERING CHILDREN
	115 CASES	30 CASES
19-24	14	7
25-29	35	12
30-35	48	11
36-39	15	—
40-46	3	—

It is true in general that the younger the patient, the better is the outlook for subsequent pregnancy. Table IV indicates that this statement also applies to this series.

The possible bearing of age upon the outlook for symptomatic relief was studied. The ages of the cases previously classed as "relieved," "partially relieved," or "failure," fell into essentially parallel age groups, from which it is inferred that no correlation between age and prognosis for symptomatic relief can be shown in this series.

Symptomatology.—The incidence of symptoms in the series elicited by history before operation is tabulated in the first column of Table V. The number of patients in each of the three groups, previously classed as "relieved," "partially relieved," or "failure," who complained of the particular symptom is tabulated in the remainder of Table V.

TABLE V. SYMPTOMATOLOGY

SYMPTOM	NO. OF CASES	NO. OF CASES IN EACH GROUP HAVING THE SYMPTOM					
		RELIEVED:		PARTIALLY RELIEVED:		FAILURE	
		68 CASES		29 CASES		41 CASES	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Dysmenorrhea	75	35	51.4	11	37.9	29	70.7
Low abdominal pain	59	26	38.2	15	51.7	18	43.9
Backache	35	17	25.0	6	20.7	12	29.3
Abnormal bleeding	26	14	20.6	4	13.8	8	19.5
Sterility	18	12	17.6	4	13.8	2	4.9
Headache	14	6	8.8	2	6.9	6	14.6
Nausea, vomiting	9	7	10.3	1	3.5	1	2.4
Pelvic pain	8	5	7.4	1	3.5	2	4.9
Dyspareunia	7	5	7.4	0		2	4.9
Rectal pain	5	2	2.9	1	3.5	2	4.9
Bladder symptoms	3	1	1.5	1	3.5	1	2.4

4. The prognosis for symptomatic relief and future pregnancy does not seem to be affected by age, symptomatology, the location and extent of the disease, or the magnitude of the conservative operation performed.

Conclusion

A conservative procedure can be recommended, even in the presence of a considerable amount of endometriosis.

The author wishes to thank Drs. George Van S. Smith and Arthur T. Hertig for their help in the preparation of this paper, and Dr. George W. Corner, Jr., for his review of pathologic material.

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in which the ovaries are negative. Dense adhesions and a large amount of endometriosis are more common in cases of ovarian involvement plus pelvic endometriosis. The bowel was not involved to a significant extent in any case.

One hundred six cases showed ovarian endometriosis; in twenty-three of these cases, this lesion was bilateral. The degree of ovarian involvement is indicated by the fact that resection of the lesion, with preservation of ovarian tissue on the affected side, was possible in 77 instances. In the remaining 52 instances, oophorectomy or salpingo-oophorectomy was performed. In the 52 cases in which the operation included either oophorectomy or salpingo-oophorectomy, the latter procedure was carried out 32 times, which indicates the frequency of tubal involvement. In this connection, there were two cases of ruptured tubal pregnancy in which endometriosis was an incidental finding. The gross diagnosis at operation of ovarian (unilateral or bilateral) and pelvic endometriosis was confirmed histologically in all but seven lesions. These were small implants treated by fulguration.

The operative procedures listed in Table VI were combined with suspension of the uterus in all but 8 cases. Incidental appendectomy was performed in 33 cases. Anterior colporrhaphy, perineorrhaphy, and herniorrhaphy (inguinal, femoral, and incisional) were included in a few cases. Presacral neurectomy was performed in 19 cases; of these, 13 were relieved of symptoms, three partially relieved and three were failures. There was no operative mortality in the series.

The results in symptomatic relief and subsequent pregnancy are recorded for each of the five classes in the series (Table VI). No significant difference can be shown in these results between those with minimal endometriosis and a minor operative procedure at one extreme, and those with a considerable amount of the disease and a comparatively extensive procedure at the other. The cases showing negative ovaries and pelvic endometriosis (Class I) had in many instances only a few small implants and no adhesions. The results in this class are not significantly different from the results in the series as a whole, in that, while approximately 10 per cent more cases were relieved, there were 5 per cent more failures and 3 per cent less pregnancies. The results in the 23 cases of bilateral ovarian endometriosis (Classes 4 and 5 combined) are as follows: Relieved 43.5 per cent, partial relief 26.4 per cent, failure 30.1 per cent, subsequent pregnancy 27.8 per cent. These results are essentially the same as those in the series as a whole. The results in the twelve cases showing the greatest amount of endometriosis in the series (Class 5) are slightly better than the results in the series as a whole.

Thus, no correlation can be shown between the amount and location of endometriosis and postoperative symptomatic relief and future pregnancy. One might infer, however, that the presence of a considerable amount of endometriosis is not a contraindication, from the point of view of prognosis, to a conservative operation.

Summary

1. One hundred thirty-eight cases of pelvic endometriosis, treated by laparotomy which conserved childbearing ability, are reviewed.

2. Sixty-eight of these cases, or 49.3 per cent, were relieved of symptoms; 29, or 21 per cent, were partially relieved; and 41, or 29.7 per cent, were failures, requiring later radical surgery or radiation.

3. One hundred twelve patients in the series were married and under 40 years of age; of these, 30, or 26.8 per cent, delivered a total of 39 living children. The average interval between operation and delivery was 2.7 years.

It should be noted that the two patients over 50 years of age had retroflexed uteri associated with prolapse and the suspension was done in addition to repair. This was during the earlier years, when such a combined operation was in vogue. This combined operation is not done now in our department.

TABLE II. PREVIOUS PREGNANCIES

PREGNANCIES	NO. OF PATIENTS
0	9 (2 unmarried)
1 to 3	25
4 to 8	10

TABLE III. SYMPTOMS AT TIME OF OPERATION

SYMPTOMS	NO. OF CASES
Pain in iliac region or regions	29
Discharge per vaginam	21
Backache	15
Dysmenorrhea	10
Dyspareunia	4
Menorrhagia	3
Sterility	3

There is considerable overlapping (since the total does not add up to 44), but this is due to the fact that some cases had more than one symptom.

TABLE IV. ASSOCIATED CONDITIONS

CONDITIONS	NO. OF CASES
Cervical erosion	8
Cervicitis	4
Cervical laceration	5
Ovarian cyst (simple follicular)	2
Fibroids	2
Benign uterine bleeding	3
Cystocele	2
Relaxed perineum	2
Anxiety syndrome	1

Here again there is overlapping because some cases had more than one associated condition. (Total number with associated conditions 24.)

TABLE V. OPERATIONS PERFORMED (IN ADDITION TO THE 44 SUSPENSIONS)

OPERATIONS	NO. OF CASES
Cauterization of cervix	11
Repair of cervix	5
Oophorectomy	2
Enucleation of fibroids	2
Curettage	3
Perineorrhaphy	2
Presacral sympathectomy	3
Appendectomy	9

There were 24 patients who had operations in addition to suspensions so that the overlapping here is due to the fact that some had more than the two operations.

Results of Inquiry

A. Cases of Uncomplicated Retroflexion.—

There were 14 patients who had suspensions only and 6 cases in which an appendectomy was done in addition to the suspension (the appendix ap-

A Review of Cases

(From the Department of Obstetrics and Gynaecology, Dalhousie University)

A total of 93 cases was accumulated. This figure represents all of the cases on which complete records were available, and all were operated upon in the Victoria General Hospital, Halifax, Nova Scotia, by the members of this Department only, who, therefore, had similar technique and standards. Follow-up letters were sent and the questionnaire was essentially of this nature (no leading questions asked).

1. Did the operation on-----cure your symptoms (enumerated)?
date
Yes? No? If so, for how long?
2. Did you have any children since operation?
Yes? No? How long after operation was first one?
3. Did you have any miscarriages since operation?
Yes? No? How long after operation was first one?

Conditions at Time of Operation

TABLE I. AGE OF PATIENTS

AGE IN YEARS	NO. OF PATIENTS
18 to 30	28
31 to 40	10
41 to 50	4
Over 50	2

4. Number of patients with fibroids on whom enucleation was done in addition to suspension - - - - - 2
Complete relief - - - - - 2
Symptoms: sterility, iliac pain.

Here, again, if we can rightly say that the operation cured the sterility, then we must remember that this symptom may well have been due to the fibroids and with their enucleation pregnancy supervened, rather than because of the suspension. It should be noted here that these patients became pregnant six to eight years following the operation so can one say it was due to either part of the operation?

5. Number of cases in which a curettage was done in addition to suspension - - - - - 2
Complete relief: menorrhagia - - - - - 1
Partial relief - - - - - 1
Relief of symptoms for 2 years: menorrhagia.
No relief of others: backache.

Here again, possibly the curettage, and not the suspension cured the menorrhagia.

6. Number of cases associated with marked dysmenorrhea and anxiety for which a presacral sympathectomy was done in addition to suspension - - - - - 2
No relief - - - - - 2

Symptoms: discharge, dysmenorrhea, menorrhagia, iliac pain.

(In both cases nerve fibers were found in the material removed.)

7. Number of cases associated with ovarian cyst in which oophorectomy was done in addition to suspension - - - - - 1
No relief - - - - - 1

Symptoms: backache.

8. Number of cases associated with prolapse (cystocele) in which a repair was done in addition to suspension - - - - - 2

Complete relief - - - - - 2

Symptoms: backache, discharge, iliac pain.

In this group the cystocele may well have caused these symptoms, and the relief obtained may have been due to the repair and not necessarily the suspension.

9. One patient had many operations in addition to suspension (appendectomy, oophorectomy, curettage, cauterization, presacral sympathectomy).

Complete relief - - - - - 1

Symptoms: discharge, backache, menorrhagia, and iliac pain.

With this type of shotgun procedure any one of the operations could have relieved the complaints.

TABLE VIII. SUMMARY OF RELIEF OF SYMPTOMS IN SECTION B (WHERE OTHER OPERATIONS WERE PERFORMED IN ADDITION TO SUSPENSION FOR ASSOCIATED CONDITION)

DEGREE OF RELIEF	NO. OF CASES	SYMPTOMS RELIEVED	SYMPTOMS NOT RELIEVED
Complete	14	Iliac pain, backache, discharge, dysmenorrhea, sterility, menorrhagia	—
Partial*	4	Iliac pain, discharge, dysmenorrhea, menorrhagia, sterility	Iliac pain, backache, dysmenorrhea
None	6	—	Iliac pain, backache, discharge, dysmenorrhea, menorrhagia

*Partial relief indicates relief of some symptoms for from two years to present but no relief of other symptoms.

parently normal from the pathologic reports and removed only as a routine). Therefore, there were 20 cases of uncomplicated retroflexion and the results in these are tabulated in Table VI.

TABLE VI. RELIEF OF SYMPTOMS BY SUSPENSION ALONE

DEGREE OF RELIEF	NO. OF CASES	SYMPTOMS RELIEVED	SYMPTOMS NOT RELIEVED
Complete	7	Iliac pain, backache, dysmenorrhea, deep dyspareunia	—
Temporary*	2	Iliac pain, backache, discharge	All symptoms recurred after one to five years
Partial†	7	Iliac, pain, backache, discharge	Iliac pain, discharge, sterility, dysmenorrhea
None	4	—	Iliac pain, deep dyspareunia

*Temporary relief indicates complete relief of symptoms for 1 to 5 years.

†Partial relief indicates relief of some symptoms for from 6 months to present but no relief of other symptoms.

It can readily be seen that only 7 cases of the 20 (i.e., 35 per cent) had complete relief of all their symptoms while the remaining 13 (i.e., 65 per cent) had little or no relief. Further, there was no consistency as between which symptoms were relieved and which not.

B. *Remaining Results* (where other operations for definite lesions were performed in addition to the suspension).—

1. No. of cases with cervicitis and/or erosion in which, in addition to suspension, a cauterization was done - - - 10. Results tabulated in Table VII.

TABLE VII. SUSPENSION PLUS CAUTERIZATION OF CERVIX

DEGREE OF RELIEF	NO. OF CASES	SYMPTOMS RELIEVED	SYMPTOMS NOT RELIEVED
Complete	6	Iliac pain, backache, discharge, dysmenorrhea	—
Partial	1	Sterility	Dysmenorrhea
None	3	—	Iliac pain, discharge, dysmenorrhea

Here again there is a definite lack of consistency in the relief of symptoms with the exception of backache. But it is quite obvious that one cannot attribute the relief of backache to the suspension because the original cause may well have been the erosion or cervicitis and thus the backache was relieved by the cauterization.

2. Number of cases with laceration of cervix on which, in addition to suspension a trachelorrhaphy was done - - - 2
 Partial relief - - - - - 2
 Relief of some symptoms for 2 to 3 years: discharge, dysmenorrhea, iliac pain; but no relief of other symptoms: backache, iliac pain.

3. Number of cases associated with laceration of cervix and relaxed perineum on which both a trachelorrhaphy and perineorrhaphy were done in addition to suspension - - - - - 2
 Complete relief - - - - - 2
 Symptoms: backache, discharge.

In this group one cannot attribute the relief of symptoms to the suspension because the backache may well have been due to either or both the laceration and the relaxed perineum and the discharge due to the laceration, so that the trachelorrhaphy and perineorrhaphy may well have been the reason for the relief of the symptoms.

The retroverted uterus has proved a constant source of surprise to us. This is the sort of thing by which we are nonplussed: A patient comes into our service who has been with us before. Some years ago we did a suspension for a retroverted uterus. She is now back for something altogether different. The suspension, she tells us, was a complete success and she has never had symptoms due to the retroversion since. Yet we find on examination that the uterus is back in the same position it was before we suspended it. Another woman on whom we have done a suspension gets complete relief of her symptoms for some years. But they recur. She is convinced that the retroversion has also recurred. So she is admitted to hospital prepared to have another suspension. We find on examination that the uterus is nicely anteverted. Here is another woman with symptoms suggesting a retroverted uterus. On examination she has a retroverted uterus. We do not operate on her. We see her several times and she still has the retroversion. Then another doctor sends her in again for operation, and we find that the uterus in the meantime has anteverted itself (but she still has all the symptoms). Another woman has a retroverted uterus that appears to be causing some symptoms. We insert a Hodge pessary after anteverting the uterus under anesthetic. She comes back in three months with all her symptoms gone, but as a result of family manipulations the pessary has got turned over on its side, the uterus has returned to its ancient retroversion. Or here is another woman who gets complete relief of her symptoms as a result of suspension until her husband leaves her, when they all recur, yet the uterus has remained anteverted. It is this sort of thing, coupled with the general results stated in this paper, that have led us to wonder if the retroverted uterus can justifiably be blamed for any symptom other than that type of deep dyspareunia where the ovary gets caught between the retroverted uterus and the banging penis.

Conclusion

We thus cannot say that, in our operative experience at the Victoria General Hospital, suspension has played a really satisfactory part in the cure of uncomplicated retroversions. The number of complete cures has been so small as to cause us to ask ourselves if the suspension in such cases did not act psychologically rather than somatically. Furthermore, the lack of consistency in the symptoms cured, or not cured, is so outrageous that we doubt the validity of blaming any of them on the retroverted uterus. In short, we are left in a state of complete skepticism with regard to the retroverted uterus as a producer of symptoms, and of suspension as a cure for such symptoms.

As a result of this we now do not do a suspension except under these conditions: (a) the uterus is anteverted, if necessary under Pentothal anesthetic, (b) a Hodge pessary is inserted and left in for three months, (c) the pessary is removed and left out for a month. If, as a result of the insertion of the pessary, the symptoms are relieved, and if they recur when the pessary is removed, we feel that the operation might be justified—but we have had it fail to cure even in cases where such precautions were taken. We believe, nevertheless, that the operation should never be done until the pessary has been used in the manner just indicated.

I am greatly indebted to Dr. H. B. Atlee, Chief of the Department of Obstetrics and Gynaecology, and to Dr. C. B. Stewart, Professor of Epidemiology, Dallhousie University, for their suggestions and advice in the preparation of this paper.

In this section, 14 cases (59 per cent) experienced complete alleviation of their symptoms while 10 cases (41 per cent) had little or no relief. This was not significantly better than the results in Section A, and, further, as has been pointed out above, the other operations performed in addition to the suspensions were probably responsible for the cure of many of the symptoms.

The number of complete cures in the foregoing series seems unrewardingly small. Furthermore, there was a marked lack of consistency in the relief of symptoms.

Our results also throw skepticism on the indications for suspension in uncomplicated retroflexion usually given in the textbooks, namely: habitual abortion, sterility, iliac pain, backache, and dysmenorrhea.

Habitual Abortion.—Of the 44 patients, only 2 gave a history of more than one abortion, both of these having had 5:

(a) The first one was a woman, aged 37 years, who had had one full pregnancy (thirteen years) and then five abortions before the suspension (the last one having been one year prior to the operation). Since the uterus was suspended (plus cauterization of cervix for cervicitis) patient has not been pregnant, seventeen years after operation.

(b) The second patient was a woman aged 32 years, who had had three full pregnancies (seven years to four years), and then five abortions in two years, prior to the operation. Since the suspension in 1935, patient has had three full pregnancies (the first one one year after operation), and then had two abortions since the full pregnancies to date. The net result seems to be similar to the condition before operation, although it would appear that the suspension might have relieved the situation for a short time.

So, in the only two cases of habitual abortion in our series, one had no proved relief, the other had only a partial, if any, degree of success.

Sterility.—In the case of sterility, only seven (married) of the 44 patients had not had children previous to the operation and of these only three had actually complained of the condition:

(a) One of these three had a simple retroflexed uterus and she has not become pregnant yet (10 years).

(b) The other two had associated fibroids which were enucleated. These became pregnant six to eight years postoperatively, respectively. In these cases one can surely not attribute the successful pregnancies to either the suspension or the enucleation of the fibroids.

Of the four patients who did not complain of sterility, only one has become pregnant to date, her first pregnancy having been one and one-half years after the operation. In this case, first, we are not sure how long she was married before the operation (she was 27 years old), and, second, it took a year and a half after the suspension before impregnation occurred. Surely, we cannot claim that the pregnancy in this case was due to the operation. Furthermore, I am informed by a member of our staff that he has done fourteen suspensions, where uncomplicated retroflexion was the only condition found as between husband and wife. In only one case did the patient become pregnant in a sufficiently short time to lay it to the operation, and that a woman who had previously had children.

Iliac Pain.—Of the 20 patients with uncomplicated retroflexion (in 6 of whom a routine appendectomy was done), 13 complained of iliac pain, of whom 8 obtained complete relief, 2 of these having had an appendectomy.

Backache.—Of the same 20 patients, 10 had backache, of whom 6 got complete relief.

Dysmenorrhea.—Of the same 20 patients, only 2 complained of this symptom, of whom one got relief.

On admission, physical examination revealed an apprehensive, slender woman, who was extremely dyspneic and orthopneic. The respiratory rate was 52, the temperature was 101° F., the pulse rate was 138, and the blood pressure was 120/70. There was pallor of the skin and mucous membranes, but no icterus. The neck veins were not distended. The breasts were engorged. Both sides of the chest were filled with many coarse bubbling râles, extending from the apices to the bases, anteriorly and posteriorly. The apical impulse of the heart was in the fifth intercostal space, just inside the mid-clavicular line. There was a soft systolic murmur at the apex and at the pulmonic area. The uterus was enlarged to the size of a seven-month gestation. Fetal heart sounds were audible in the right lower quadrant. Examination of the extremities revealed marked bilateral calf-muscle tenderness along the course of the deep veins in the calves. There was tenderness in the adductor group of muscles of both thighs. Homans' sign was positive bilaterally.

Treatment was immediately started and consisted of oxygen by mask, bloodless phlebotomy, intravenous hypertonic sucrose, papaverine, and aminophylline. The patient responded favorably, and within an hour, the respiratory rate had returned to normal, and a few râles remained at both bases. She was not digitalized.

The urine was normal; the red blood count was 3,000,000 with a hemoglobin of 7.0 Gm. per cent; the white blood count was 9,200 with 65 per cent polymorphonuclear leucocytes, 6 per cent band metamyelocytes, 20 per cent lymphocytes, 6 per cent monocytes, 2 per cent eosinophiles and 1 per cent basophiles; mean corpuscular volume was 80 cu. microns; mean corpuscular hemoglobin was 23 micro-micrograms; mean corpuscular hemoglobin concentration was 29 per cent; the blood smears showed a hypochromia, nucleated red cells, and target cells; there was no increased fragility of the red cells to hypotonic saline; the sickling preparation was negative; stools were repeatedly negative for ova and parasites; the Mazzini test of the blood for syphilis was negative; blood type was O, Rh positive; the albumin-globulin ratio was 4.5/2.0; the icteric index was 5; the nonprotein nitrogen was 28 mg. per cent; the cephalin flocculation test was positive during pregnancy, but subsequently remained persistently negative. An x-ray of the chest, taken the day after admission, showed clear lung fields, and a heart that was normal in size and shape. The electrocardiogram was normal.

A diagnosis was made of bilateral phlebothrombosis of the deep veins of the leg with pulmonary embolism, and anticoagulant therapy was started. Heparin was given intravenously in 100 mg. doses every six hours for eight doses, and dicumarol was given orally in doses of 200 mg. for the first three days, and then in accordance with the prothrombin time, as shown in Figs. 1 and 2. The prothrombin time was determined by the Link-Shapiro modifications* of the Quick method.

The patient continued to have signs of deep vein thrombosis in the legs and thighs. However, examination of the chest remained negative. On the sixth hospital day, she was given a transfusion of 500 c.c. of blood, because of the anemia. Ferrous sulphate had already been started orally. By the eleventh day, her red blood count was 3,980,000 and the hemoglobin was 7.25 Gm. per cent. Clinically, she was much improved. The signs in her legs had disappeared, and on the fourteenth day, it was decided to decrease gradually the dosage of dicumarol, preliminary to discharging the patient.

A second transfusion of 500 c.c. of blood was given on the 19th hospital day. The prothrombin time was now near normal. On the 20th day, she suddenly became dyspneic and developed severe pleuritic pain in the left chest anteriorly and posteriorly. There was no evidence of recurrence of phlebothrombosis in the veins of the legs. A diagnosis of a second pulmonary embolus was made. The chest roentgenogram revealed the heart enlarged in the transverse diameter due to elevation of the diaphragms, and chronic passive congestion was evident in both lung fields, more marked at the right base. Dicumarol was again started, and it was planned to continue the drug until the onset of labor, and to resume anti-coagulant therapy after delivery. Because of the possible ill effects of dicumarol on the fetus, and the question of uterine hemorrhage at the time of delivery, it was decided to keep the prothrombin time on the low side (30 seconds) of the usually accepted therapeutic

*Thromboplastin was kindly furnished by Dr. Walter Hoskins of the Maltine Company.

DICUMAROL IN THE TREATMENT OF ANTENATAL THROMBO-EMBOLIC DISEASE

Report of a Case With Hemorrhagic Manifestations in the Fetus

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THE use of dicumarol during the postpartum period has been established as a safe method of therapy for venous thrombosis, without inducing uterine bleeding.^{1, 2} Barnes and Ervin² have used the drug prophylactically during labor with no untoward effect, and anticoagulant prothrombin levels were not reached until after delivery. Similar results have been obtained by Allen and his group³ in the treatment of venous thrombosis and pulmonary embolism following delivery.

Because of the infrequency of antenatal thromboembolic disease, little is known of the effect of dicumarol on the human fetus. However, the earliest reports on sweet clover disease in cattle demonstrated the increased susceptibility of the new-born calf to this hemorrhage producing agent.^{4, 5, 6} Schofield⁴ described a calf, born of a cow fed spoiled sweet clover hay, that developed typical hemorrhagic symptoms within a few hours after birth and died, while the mother remained well. Roderick⁵ noted that an active well-developed calf, born of a cow fed for thirteen days on damaged sweet clover, died of hemorrhage twenty-eight hours after birth. In a study on newborn pups of a pregnant dog given dicumarol before parturition, Quick⁷ found that out of a litter of seven, the four pups not treated with vitamin K died of hemorrhage, whereas the pups that received vitamin K survived.

It would appear possible, as Quick⁷ surmised, that similar hemorrhagic tendencies might appear in the human fetus following the antenatal use of dicumarol. The case which follows represents the first known experience at Bellevue Hospital of the hemorrhagic effect of dicumarol on the fetus of a mother receiving prolonged therapy with this drug for the control and treatment of thrombo-embolic disease.

Report of Case

O.S., a 23-year-old Puerto Rican multipara, was admitted to the emergency medical ward of Bellevue Hospital on July 25, 1947, during the seventh month of her pregnancy, in acute respiratory distress. Her illness began four days previously with the sudden onset of pleuritic pain in the left chest, and dyspnea. This was associated with cough and fever, but no hemoptysis. The thoracic pain continued, and the dyspnea became progressively more severe, finally requiring hospitalization.

Her two previous pregnancies in 1943 and 1944 were uneventful, except for the presence of an associated anemia. She denied any knowledge of heart disease. Her last menstrual period was December 23, 1946. During the few months preceding the present illness she had noted recurrent pains in both calves, the soles of both feet, and in the medial aspects of both thighs.

values. By the 23rd day, the thoracic pain had disappeared, and the patient was feeling well again. Repeated blood cultures were negative. There was no evidence of specific organic heart disease, but, in view of the episode of pulmonary edema, in association with the embolic episode on admission, digitalis was started. The patient was now ambulatory on the ward. On the 40th day, the red blood count was 3,540,000 and the hemoglobin was 10.3 Gm. per cent. On the 44th day, she noted pain above the mid-point of the left inguinal ligament. There was tenderness to deep palpation in this area, and a diagnosis of pelvic vein thrombosis was considered. At this time, the prothrombin time was 35 seconds. On the 48th day, she developed severe pain in the precordial region, which radiated to the left shoulder and arm, associated with dyspnea. A diagnosis was made of another pulmonary embolus. There was tenderness on pressure over the medial aspects of both thighs. On this day, the prothrombin time had been inadvertently allowed to fall to $21\frac{1}{2}$ seconds. The following day, she appeared worse. The precordial pain was severe, and the dyspnea was marked. The patient was placed in an oxygen tent and given aminophylline, morphine, and papaverine, and by the next day, was much improved. She continued to be well until the 51st day, when she developed false labor pains which lasted for several hours. Two days later, on the 53rd day, the fetal heart became inaudible. There had been no previous indication of fetal distress. She was kept on dicumarol until the 73rd day, when labor began. Vitamin K, 60 mg., was given intravenously, and $21\frac{1}{2}$ hours later she delivered a $6\frac{1}{2}$ pound macerated stillborn baby boy. At delivery, the prothrombin time was $17\frac{1}{2}$ seconds (normal = 14-17 sec.). There was no bleeding during the third stage of labor, and the usual oxytocics were given.

Several hours after delivery, the patient had a chill and the temperature rose to 103.8° F. She became dyspneic and cyanotic and again required an oxygen mask. Although examination of the chest was negative, another pulmonary embolus was suspected, and heparin and dicumarol therapy were resumed in doses as shown in Fig. 2. The patient improved rapidly, and the remainder of the postpartum course was uneventful. A roentgenogram of the chest made several days after this episode showed a wedge-shaped area of pulmonary consolidation extending from the left hilum to the first interspace, and prominence of the pulmonary artery.

The uterus involuted normally, and thrombosed pelvic or broad ligament veins could not be felt on bimanual examination. Dicumarol was continued for ten days after delivery and on the 14th postpartum day, the patient was discharged to the clinic. She has been followed for a period of four months after delivery and has been well. Examination of the heart has revealed essentially normal findings. The murmurs described on admission were still present, but of decreased intensity. The x-ray of the chest and electrocardiogram were normal. Her red blood count was 3,750,000, and hemoglobin was 13.3 Gm. per cent.

In summary, a 23-year-old multipara was admitted in the seventh month of pregnancy with a diagnosis of phlebotrombosis and pulmonary embolism. Because of three additional episodes of pulmonary embolism, each occurring as the prothrombin time was allowed to approach normal, it was necessary to continue dicumarol therapy through the last two months of pregnancy and the postpartum period. Intrauterine fetal death occurred on the 53rd hospital day, and on the 74th day, she delivered a stillborn macerated fetus.

Pathologic Examination of the Fetus

The body was that of a 2,640 Gm., 49 cm., badly macerated white male infant.

Head: There was considerable softening and overriding of the skull bones. Upon opening the skull, a large cephalohematoma was noted overlying both parietal bones. The brain was very mushy in consistency and a dull brown color throughout. There was no evidence of intracranial hemorrhage.

Chest: Upon the opening of the chest, extensive hemorrhage into the thymus gland was noted. The thymus was enlarged to about 4 by 4 by 4 cm. and was practically replaced by blood clot.

Heart: The pericardial sac contained about 15 c.c. of bloody fluid. The pericardium was normal. The myocardium was a dull light-brown color and the endocardium was normal.

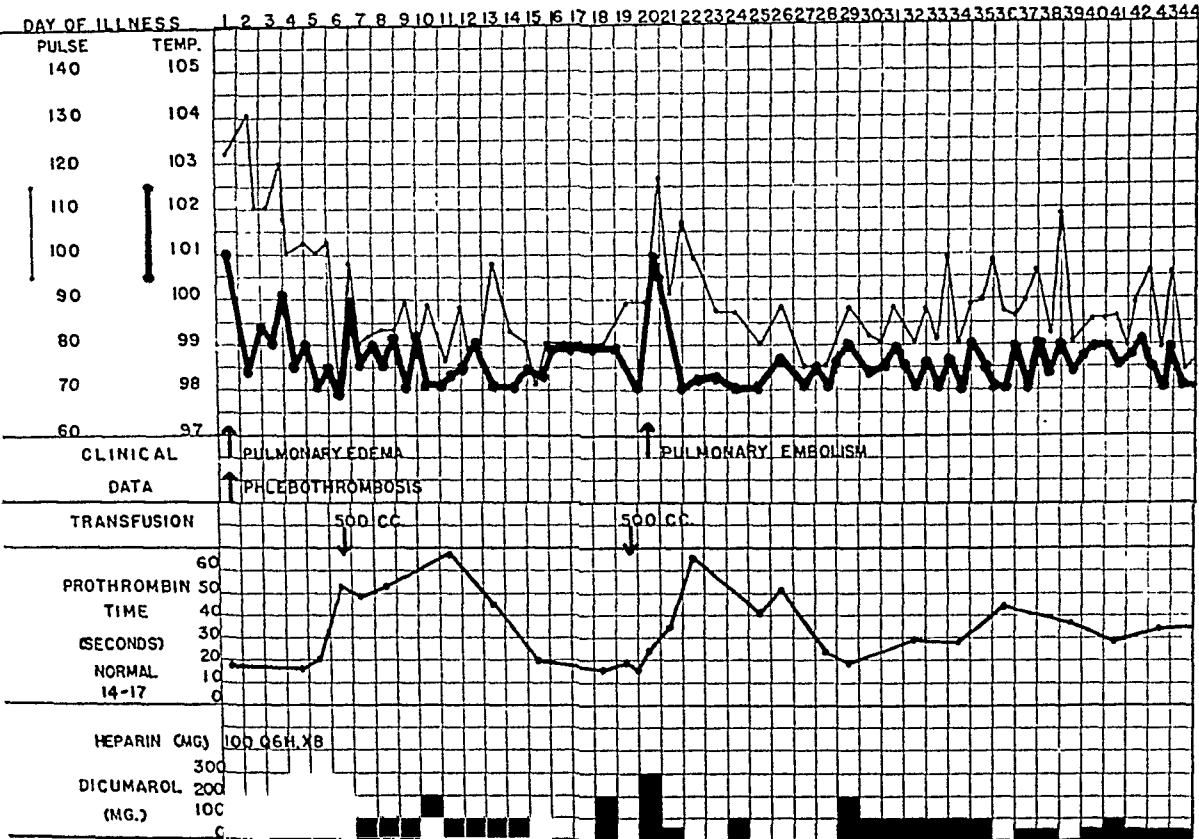


Fig. 1.—Clinical course.

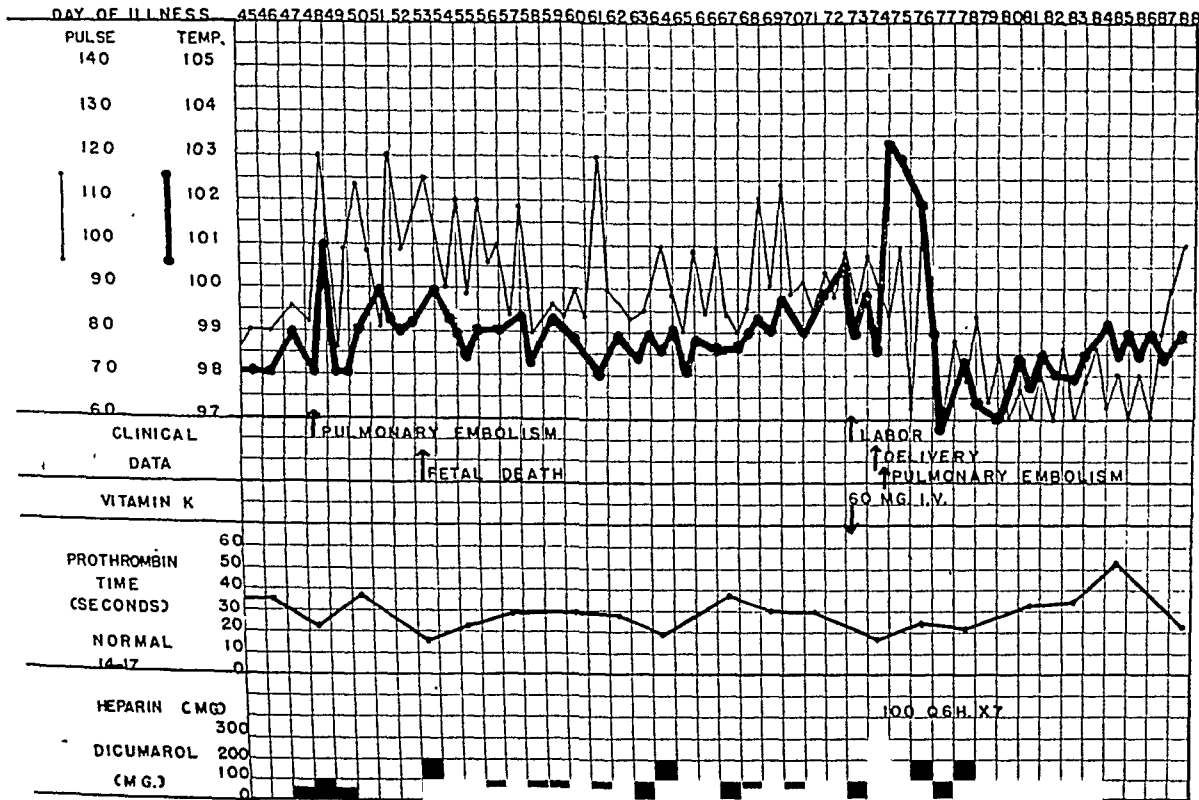


Fig. 2.—Clinical course (continued).

episode on the 20th day occurred at a time when dicumarol was purposely being reduced with a view to discontinuing it entirely. The episode on the 48th day occurred when the level was inadvertently allowed to return to normal, and the third embolus occurred a few hours after delivery, when the level again was normal, due to vitamin K administration. The embolus on the 20th day raises the question as to when anticoagulant therapy may be safely discontinued, and this is difficult to determine. From the clinical course, it would seem that anticoagulant therapy in this patient was necessary throughout the entire antepartum and postpartum period. The embolus of the 48th day and of the 74th day demonstrate again the importance in anticoagulant therapy of steering a safe course between hemorrhagic and coagulation levels. In this patient, embolization apparently occurred each time that the prothrombin level approached normal.

The absence of bleeding during delivery is noteworthy. The administration of 60 mg. of vitamin K intravenously at the onset of labor was able to return the prothrombin time to $17\frac{1}{2}$ seconds at the time of delivery, $21\frac{1}{2}$ hours later. Whether the absence of bleeding was due to the vitamin K, or to changes which occurred in the vessels of the placental-uterine junction, due to fetal death twenty-one days prior to delivery, is difficult to ascertain.

The question of venous ligation as the treatment of choice in this patient was considered. On her admission, the thrombotic process had already involved the deep veins of the thigh, and several examiners suspected pelvic vein thrombosis. This would have necessitated a high ligation, possibly of the vena cava, a procedure of considerable technical difficulty in the presence of pregnancy, if not entirely contraindicated, due to its possible untoward effect on the uterine circulation. Walsh and Barone⁹ have reported two cases of antenatal phlebothrombosis, one with involvement of the left long saphenous and femoral veins, the other with involvement of the right long saphenous vein. Both patients were treated successfully with thrombectomy and ligation with uneventful recoveries. However, a search of the literature has failed to reveal any cases of antenatal phlebothrombosis that were treated with high venous ligation (high femoral, iliac, or vena caval), so that the effects of these procedures in the presence of pregnancy must be considered as unknown.

On the basis of our experience with this case, it is not possible to formulate a definite policy with regard to therapy for thrombo-embolic disease complicating pregnancy during the antenatal period. However, the danger to the fetus of prolonged therapy with dicumarol can be pointed out, since maternal prothrombin levels cannot be used as an index of the response of the fetus to this drug. Whether dicumarol can be used safely for a shorter period of time than in this case is not known. Whether prolonged therapy with heparin is equally dangerous to the fetus has not, to our knowledge, been determined.

Summary

1. A case of recurrent thrombo-embolic disease, occurring in a pregnant woman during the last two and one half months of her gestation, is reported.

Lungs: Both pleural cavities contained about 100 c.c. of dark bloody fluid. The lungs were retracted and rubbery in consistency. On section, there was no evidence of aeration. The surface was a uniform dark-red color.

Abdomen: The liver, spleen, pancreas, adrenals, and kidneys showed no evidence of hemorrhage, but were very soft in consistency. There was no hemorrhage in the gastrointestinal or genito-urinary tracts.

Microscopic Examination.—

Lungs: The alveoli were nonexpanded, and numerous areas were seen where the alveolar mass contained epithelial debris and epidermoid type of cells. Areas of focal hemorrhage were present.

Thymus: The architecture of the thymus gland was completely disturbed by hemorrhage. The hemorrhage extended outward through the capsule and the entire gland was surrounded by diffuse hemorrhage. The normal architecture of the individual lobule was markedly disturbed by the extensive hemorrhage, so that the cells making up the gland were irregularly dispersed about the periphery of the lobule.

The remainder of the organs showed extensive autolytic changes.

Anatomical Diagnosis.—Massive hemorrhage of the thymus gland; focal hemorrhages of the lungs; bilateral hemothorax; hemopericardium; slight pulmonary aspiration of amniotic fluid; maceration with congestion and autolysis of all organs.

Discussion

On the basis of animal studies, already cited, it seems reasonable to assume that the fetal death was due to hemorrhage secondary to dicumarol. The findings at necropsy differed sufficiently from those usually found in the stillborn, following intrauterine asphyxia, to indicate an unusual cause for the fetal death. There appears to be little doubt that the extensive hemorrhage noted in the fetus was a direct effect of prolonged dicumarol therapy during the antenatal period. The mother had been maintained on dicumarol for fifty-three days prior to fetal death, and had received a total of 3,750 mg. of dicumarol.

Throughout the course, with few exceptions, the majority of the prothrombin time determinations were between 25 and 35 seconds. None of the determinations were abnormally high, and at no time did the patient show evidence of hemorrhagic phenomenon. Hence, it would seem that the fetus is more susceptible to the drug than the mother, and that maternal prothrombin determinations are not indicative of the fetal response to dicumarol. Quick⁷ has previously pointed out this difference in susceptibility in the dog.

Two diagnostic features of thrombo-embolic disease were missing in this case. Hemoptysis was absent, and there was no roentgenographic evidence of pulmonary infarction until after delivery. Nevertheless, the patient on admission had typical signs and symptoms of phlebothrombosis, which had extended to the deep veins of the thigh. During the antenatal period, she was considered to have had episodes of pulmonary embolism, without infarction. However, the wedge-shaped shadow in the postpartum x-ray of the chest was characteristic of pulmonary infarction and confirmed the diagnosis of thrombo-embolism at least on this occasion.

An analysis of the clinical course (Figs. 1 and 2) reveals that the three pulmonary emboli which occurred while the patient was in the hospital developed on days when the prothrombin time had returned to normal. The

AN ANALYTICAL SURVEY OF MULTIGRAVIDAS

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THIS paper deals with those patients who have had six or more pregnancies and is offered to refute the false feeling of security in the management of multigravidas. Dr. Bethel Solomons, in his paper, "The Dangerous Multipara,"¹⁰ has stressed the numerous and occasionally serious implications of the various complications which are encountered in any large series of multiparous patients. The various assaults of successive pregnancies on the maternal organic systems and the residual pathology produced by preceding illnesses, all help to make the multigravida a poor risk. In this paper we have analyzed 783 pregnancies, parturitions, and puerperia of 500 multigravidas delivered at the Elizabeth Steel Magee Hospital, Pittsburgh, Pennsylvania, for the five-year period from Jan. 1, 1941, to Jan. 1, 1946.

At first glance, this subject would appear to be almost entirely a ward or free-clinic problem. That the treatment of the multigravida is not limited to this group is demonstrated by the fact that 27.2 per cent of women in their sixth and subsequent pregnancies were under the care of private physicians. In other words, every fourth patient is a potential problem for the obstetrician in private practice and should be watched even more carefully than the primigravida on whom his attention is usually focused. As Dr. Solomons stated in his paper, "Pregnancy is definitely a case where practice does not make perfect."¹⁰

Gravidity

Of the 783 deliveries studied, 237 (30.2 per cent) were sextigravidas, 205 (26.2 per cent) septigravidas, 129 (16.5 per cent) octigravidas, 87 (11.2 per cent) nonigravidas, and 61 (7.7 per cent) decigravidas. The remaining 64 women had had from 11 to 25 pregnancies. This latter classification formed 8.2 per cent of the total deliveries.

GRAVIDITY

GRAVIDA	NUMBER	PER CENT
vi Sextigravidas	237	30.2
vii Septigravidas	205	26.2
viii Octigravidas	129	16.5
ix Nonigravidas	87	11.2
x Decigravidas	61	7.7
xi to xxv	64	8.2
Total	783	100.0

Types of Delivery

A total of 620 normal children resulted from the 783 deliveries with 62 additional stillbirths and neonatal deaths, and 101 abortions. There were 573

2. The patient was treated continuously with dicumarol and on the 53rd day, after receiving 3,750 mg., the fetus died in utero.

3. Pathologic examination of the fetus revealed that death was due to hemorrhage, apparently caused by dicumarol.

4. Attention is drawn to the danger of fetal death from hemorrhage, which may result from the administration of dicumarol during the antenatal period.

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is now done within six to eight hours after delivery or is postponed until complete involution of the pelvic organs has occurred.

DEATHS IN MULTIPARAS

GRAVIDA		CAUSE OF DEATH
1.	vi	Septic abortion, pelvic thrombophlebitis, pulmonary infarcts
2.	vi	Essential hypertension, cerebral accident (before delivery)
3.	vii	Tubal ligation seventh postpartum day, pulmonary emboli
4.	viii	Sulcus tear with septicemia and fulminating peritonitis, pulmonary emboli
5.	viii	Tubal fulguration ninth postpartum day, pulmonary emboli
6.	ix	Uterine atony, uncontrollable postpartum hemorrhage
7.	x	Nephritic hypertension, uremia

As we study the fetal mortality in this series, it is found that there were 62 deaths in 682 births, or 9.1 per cent. If the 12 macerated fetuses and 13 nonviable infants are deducted, the corrected fetal mortality becomes 5.4 per cent. The causes of death as indicated on the hospital charts are listed below.

FETAL MORTALITY

MULTIGRAVIDAS		HOSPITAL AVERAGE	
Stillbirths	29	4.2 per cent	2.3 per cent
Macerated stillbirths	12	1.7 per cent	1.3 per cent
Prematures (nonviable)	13	1.9 per cent	0.7 per cent
Died	21		
Atelectasis	2		
Congenital anomaly	1		
Respiratory failure	1		
Emphysema	1		
Anoxia	1		
Jaundice	1		
Septicemia—			
Cellulitis of scalp	1		
Uncorrected fetal mortality:	62 deaths in 682 births, or 9.1 per cent		7.4 per cent
Less prematures and macerated stillbirths:	25		
Corrected fetal mortality:	37 deaths in 682 births, or 5.4 per cent		5.3 per cent

It is readily noted that the percentages of stillbirths, macerated stillbirths, and nonviable prematures in the multigravidas are higher than in the hospital general average.

There were, in addition, 98 spontaneous and induced, and 3 therapeutic abortions in the 783 pregnancies studied. Without a doubt, there were other spontaneous complete abortions in this group of 500 patients which did not necessitate hospitalization.

There was then, in this series, 1 abortion to every 7.8 births, or 12.8 per cent. This figure approximates Bland and Montgomery's¹ estimate that one pregnancy in five ends in abortion.

ABORTIONS

	MULTIGRAVIDAS		HOSPITAL AVERAGE	
Spontaneous and induced	98	12.8 per cent	271	8.27 per cent
Therapeutic	3	0.38 per cent	13	0.39 per cent

Toxemias

According to the literature, the expected incidence of pre-eclampsia is from 10 to 15 per cent, and the disease is seen more frequently in primiparas. When

spontaneous births, 23 low forceps, 6 midforceps, 38 breech extractions, 25 versions and extractions, 16 cesarean sections, and 1 craniotomy with extraction.

TYPES OF DELIVERY

MULTIGRAVIDAS	NUMBER	PER CENT	GENERAL HOSPITAL*	
			NUMBER	PER CENT
Spontaneous	573	84.0	1370	41.9
Low forceps	23	3.4	1360	41.6
Midforceps	6	0.9	99	3.0
Breech extractions	38	5.6	107	3.2
Internal podalic version and extraction	25	3.7	165	5.0
Cesarean sections	16	2.3	171	5.2
Craniotomy and extraction	1	0.1	2	0.06

*Hospital averages are figured from 3,274 deliveries in the Elizabeth Steel Magee Hospital from Jan. 1, 1945, to Jan. 1, 1946.

It is to be noted that there was a considerably higher percentage of spontaneous deliveries and a greatly lower percentage of low forceps deliveries in the multigravidas. This is explained by the fact that the ward multigravidas are largely delivered by students and the general hospital figures include primigravidas, both private and ward, who are usually delivered by prophylactic outlet forceps. A higher percentage of breech deliveries in the multiparas indicates a greater frequency in these patients. The hospital general average cesarean section rate is over twice that of the multigravida section rate.

Morbidity and Mortality

The maternal morbidity is much higher in the grandipara than in the primipara and in the gravida v and under, as is indicated by the increased hospital days. The average period of hospitalization for private patients (primiparas and multiparas) over the last five-year period has been twelve days, while that for ward patients has been eight days. The average hospital stay for all patients has been 10 days. It might be stated here that hospitalization of ten to twelve days in private patients does not always indicate morbidity but merely a desire for additional rest, while, in the free clinic patient, hospitalization over the average usually indicates morbidity. The average hospital stay for multiparas, including private and ward cases, is 12.4 days. In other words, the morbidity of the multipara necessitates an increased hospitalization of 2.4 days per patient.

There is no accurate way of estimating fetal morbidity and the harm done to babies at delivery. Rank⁹ has advanced the theory that many cases of mental disease date from trauma to the fetal skull at birth.

The maternal mortality is atrociously high in that there were seven deaths in 500 mothers, or a mortality rate of 1.4 per cent. This percentage is seven times that of our average maternal mortality rate of 0.261 per cent at the Elizabeth Steel Magee Hospital (67 deaths in 25,623 deliveries from Jan. 1, 1941, to Dec. 31, 1946). This latter mortality rate compares favorably with that in other maternity centers.

MORTALITY RATES

Magee Hospital, 1941 to 1947	2.6 per 1000 births
Multigravidas, gravida vi and over	14.0 per 1000 births
Pittsburgh, Pa. ¹¹	1.5 per 1000 births
Chicago Lying-in Hospital ⁷	1.7 per 1000 births
Philadelphia, Pa., 1931 to 1933 ¹²	4.4 per 1000 births
National total, 1941 ¹²	2.7 per 1000 births

The causes of death are listed below. It will be noted that two deaths followed tubal ligation on the seventh and ninth postpartum days. Sterilization

Retained Placental Tissue

There were 13 cases of retained placenta. The placentas were removed manually either immediately following delivery or after an interval of one hour. Thirty cases of severe secondary anemia were encountered which necessitated giving 25 transfusions. Only one transfusion reaction resulted. Retained placenta occurred only slightly more frequently in multigravidas than in the hospital average, while over six times as many transfusions post partum were deemed necessary for the multigravidas as for the average hospital patient.

INCIDENCE OF RETAINED PLACENTA

	MAGEE HOSPITAL		MULTIGRAVIDAS	
	CASES	PER CENT	CASES	PER CENT
Retained placenta	34	1.0 per cent	13	1.5 per cent
Severe anemia	18	.55 per cent	30	3.8 per cent

Disproportion

There is a tendency for each successive baby to be larger than its predecessor. Usually the maternal pelvis will accommodate a slightly larger passenger, but disproportion can arise insidiously with frequent fetal injury or death.

Malpresentation

In considering malpresentations and complications of presentations, there were nine sets of twins, or one in 75 pregnancies, or an increase over the expected frequency of one in 85 to one in 100 pregnancies, as given by Bland and Montgomery⁴ and DeLee and Greenhill,⁸ respectively. Thirty breech presentations (3.8 per cent) were encountered, which is slightly more than the average incidence of 3 per cent. We find a greatly increased proportion of transverse lies with shoulder presenting. There were eight such presentations or one in 85 deliveries, which is more than twice the expected frequency of one in 200 pregnancies. Two face presentations, or 1 in 341, were encountered, which is somewhat less than the expected frequency of 1 in 200 to 1 in 300 cases. That we get anomalous presentations in the grandipara is to be expected because of an atonic uterus and the relaxed abdominal musculature so frequently found. These malpresentations, if not recognized and treated early, definitely lead to both increased fetal and maternal mortality.

Birth Weights

The average weight of a term newborn baby is generally accepted as being 7 to 7½ pounds. The average weight of the babies in this series is 7 pounds, 6 ounces, excluding prematures and twins. The largest baby in this series weighed 11 pounds, 2 ounces, and was the eleventh child of a 35-year-old mother. The smallest term baby delivered of these multigravidas weighed 5 pounds and was the ninth child of a patient with nephritic toxemia.

Length of Labor

The length of labor in multigravidas is of considerable interest and practical importance to the obstetrician. In addition, the length of labor is one indicator of the type of uterine contractions which have preceded delivery. The average length of labor in the multipara is usually considered to be about 12 hours. In our series, the shortest labor recorded was 16 minutes, while the longest labor was 96 hours and 25 minutes. The over-all average length of labor was 12 hours and 48 minutes. Arbitrarily, we have considered for purposes of comparison

pre-eclampsia does occur in multiparas, pre-eclampsia and the occasional resultant eclampsia have been said to be more severe and to offer a poorer prognosis than in the primipara. There were 49 pre-eclampsies in this series of patients, seven of whom went into true eclampsia (one or more convulsions). Two of the seven had postpartum eclampsia. There were no maternal deaths from this complication. The fetal toll was approximately 40 per cent. There were 27 cases of nephritic toxemia and 41 cases classified as essential hypertension. Possibly the latter two types of disease may be attributed partially to the increased ages of the gravidas. Mild nausea and vomiting necessitating hospitalization was not encountered. There were seven cases of pernicious nausea and vomiting (hyperemesis gravidarum), which did require hospitalization. All of these patients were treated successfully by conservative therapy. The table below gives a comparison of the incidence of the toxemias of pregnancy in multigravidas and in the Elizabeth Steel Magee Hospital. The percentage columns indicate that all of the toxemias occur in greater frequency in the multigravida than in the average hospital patient at the Elizabeth Steel Magee Hospital.

INCIDENCE OF VARIOUS TYPES OF TOXEMIAS OF PREGNANCY

TOXEMIAS	MULTIGRAVIDAS		MAGEE HOSPITAL	
Pre-eclampsia	42	5.4 per cent	79	0.24 per cent
Eclampsia	7	0.8 per cent	5	0.15 per cent
Nephritic toxemia	27	3.4 per cent	31	0.94 per cent
Essential hypertension	41	5.2 per cent	23	0.70 per cent
Hyperemesis	7	0.8 per cent	21	0.64 per cent

Placenta Previa and Premature Separation

The dangers to both mother and offspring associated with placenta previa and premature separation are well known. The frequency of placenta previa and premature separation given by various sources varies greatly. Bland and Montgomery^{2, 3} stated that one case of placenta previa is seen in every 100 pregnancies (1 per cent) and that premature separation occurs once in every 300 pregnancies (0.3 per cent). At the Elizabeth Steel Magee Hospital, in 16,737 deliveries there were 156 cases of placenta previa, or one in 107 pregnancies (0.9 per cent). There were in the same number of deliveries 211 cases of premature separation of the normally implanted placenta, or one in 79 (1.2 per cent).

In the multiparas studied, 12 cases of placenta previa, or one in 57 deliveries (1.7 per cent), and 14 cases of premature separation, or one in 48 normal births (2.0 per cent), were encountered. These figures should indicate conclusively that both of these complications are more frequent in the multiparas and especially in gravidas vi and over.

INCIDENCE OF PLACENTA PREVIA AND PREMATURE SEPARATION

	BLAND AND MONTGOMERY ^{2, 3}	MAGEE HOSPITAL		MULTIGRAVIDAS	
Placenta previa	1.0 per cent	156	0.9 per cent	12	1.7 per cent
Premature separation	0.3 per cent	211	1.2 per cent	14	2.0 per cent

With these complications, the fetal mortality is likewise appallingly high. In many instances the fetuses die in utero as a result of anoxia.

Abortion

Abortion has been discussed under morbidity and mortality.

Hydatid Mole and Ectopic Pregnancy

One hydatid mole and one ectopic pregnancy were encountered in this series. Each was handled uneventfully following accepted techniques.

labor and of sufficient severity to be recorded are listed below. All of these infections were treated either by a separate specialty clinic or by the obstetric clinic.

INFECTIONS COMPLICATING PREGNANCY AND LABOR

Amnionitis	1
Appendicitis, acute, with appendectomy	3
Bronchiectasis	1
Bronchitis	23
Cholecystitis with cholecystectomy	1
Cystitis	2
Lymphogranuloma inguinale	1
Nephritis and pyelonephritis	10
Nephrolithiasis	1
Poliomyelitis with paralysis (right leg)	1
Pneumonia	4
Psoriasis	1
Pyelitis	3
Salpingitis, chronic	1
Syphilis	27
Syphilis, meningovascular	1
Thrombophlebitis, pelvic	1
Tuberculosis	4

The infections complicating the puerperium are similarly listed below and need little explanation, except to say that they occurred in this series.

INFECTIONS COMPLICATING THE PUERPERIUM

Abscess, axillary	1
Abscess, right femoral triangle	1
Appendicitis, with appendectomy	3
Cellulitis, pelvic	1
Cystitis	2
Endometritis	18
Infarcts, lungs, septic	1
Influenza	1
Mastitis with abscess formation	14
Necrobiosis (fibroid)	1
Phlebitis	1
Pneumonia	1
Tapeworm	1

Other Complications

Besides the toxemias, hemorrhages, and infections which have already been discussed, there were certain other medical complications which were encountered. Four asthmatics had to be hospitalized during their pregnancies. The grandipara is very prone to develop painful varicosities. There were 16 cases recorded, although there must have been many more. There were 12 patients with cardiac disease, 8 cases of which were rheumatic in type. Two were in congestive failure. In this rather small group of cases there were two cases of cerebral embolus with resulting hemiplegia. Only one diabetic was encountered. Two colloid goiters were diagnosed among these patients. Two patients were diagnosed as having generalized malnutrition and emaciation. One case each of Banti's disease and idiopathic enlargement of the liver were found. One patient had an inoperable medulloblastoma of the brain. Certainly no one would say that these medical problems were improved by the added strain of pregnancy.

Multigravidity is not, per se, an indication for sterilization. In this series there were 47 postpartum ligations, seven tubal fulgurations, one tubal resection, and one hysterectomy by maternal and paternal consent.

a labor of one hour or less to be precipitate and that of twenty hours or longer to be inertial in type. There were three times as many precipitate labors in the multigravidas as were encountered in the general hospital average. On the other hand, the number of inertial labors encountered was about the same in both groups.

ANOMALOUS PRESENTATIONS, BIRTH WEIGHT OF BABY, AND LENGTH OF LABOR

	AVERAGE	MAGEE HOSPITAL		MULTIGRAVIDAS	
<i>Presentations:</i>					
Breech	3.0 per cent	107	3.2 per cent	30	3.8 per cent
Transverse ⁵	0.5 per cent	9	0.27 per cent	8	1.0 per cent
Face ⁶	0.5 per cent	9	0.27 per cent	2	0.2 per cent
<i>Birth Weight:</i>					
	7 to 7½ pounds	Unobtainable		7 pounds, 6 ounces	
<i>Labor:</i>					
	10 to 12 hours	<i>Inertial</i>		<i>Shortest</i> , 16 min.	
		504	15.3 per cent	<i>Longest</i> , 96 hours,	
		<i>Precipitate</i>		25 minutes	
		15	0.45 per cent	<i>Inertial</i>	
				102	14.9 per cent
				<i>Precipitate</i>	
				9	1.3 per cent

Because of the difficulty of determining when the grandipara is actually in labor, many are admitted in false labor with resulting useless cost to the patient and hospital. Thirty such patients in false labor were admitted for a day or so and then discharged.

Syphilis and Tuberculosis

Syphilis was found in 27 gravidas. Some of these cases were diagnosed by routine serologic examinations, while others were known syphilitics and had received more or less antisyphilitic therapy. Four patients with tuberculosis were followed very closely in our antepartum clinics and were delivered uneventfully.*

The incidence of tuberculosis and syphilis varies with the geographical location and the financial status of the group studied. Contrary to what might be expected, our ward (multigravida) incidence of tuberculosis is lower than the hospital average. This is probably explained by the fact that few tuberculous patients are physically able to have as many as six children.

SYPHILIS AND TUBERCULOSIS

	GENERAL AVERAGE	MAGEE HOSPITAL		MULTIGRAVIDAS	
	VARIES WITH LOCATION	NUMBER	PER CENT	NUMBER	PER CENT
Syphilis	3—10 per cent	89	2.7	27	3.4
Tuberculosis	1 per cent	22	0.67	4	0.51

Incidental Complications

There were 23 cases of bronchitis and upper respiratory infections which necessitated special therapy and which were noted on the hospital charts as complications. In addition, four cases of pneumonia, one case of pneumonitis, and one case of bronchiectasis complicated pregnancy and labor. Three cases of appendicitis and one case of cholecystitis necessitated appendectomy and cholecystectomy respectively. Other infections complicating pregnancy and

*The Tuberculosis League Hospital of Pittsburgh acts as our consultant in all cases of tuberculosis.

A CULTURAL METHOD FOR THE DIAGNOSIS OF TRICHOMONAD INFESTATIONS

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THE criterion of diagnosis in the symptom syndrome known clinically as "trichomonad vaginitis" has been the proper identification of the vaginal flagellate, *Trichomonas vaginalis*. There is general agreement among authors that the various clinical manifestations are easily recognized and are common.¹¹ The most frequent subjective complaint is the presence of a vaginal discharge, with an increase of vaginal discomfort prior to and following the menstrual period.⁹ The annoying and copious leucorrhea is at times watery, foaming, or frothing, and almost always malodorous. Some patients complain of mild burning on urination associated with mild frequency. These signs coupled with the demonstration of motile trichomonads in a hanging-drop preparation made from the vaginal discharge are sufficient evidence of trichomonad vaginitis for the institution of trichomonocidal therapy; however, in some instances, the persistent and refractory leucorrhea has failed to reveal the offending organisms in a wet-mount.

During the past eighteen months, an extensive research program designed to correlate varied bacterial constituents found in diverse pathological conditions of the genitourinary tract has been in progress.⁶ One major study has been directed toward symbiotic relationships between vaginal bacterial elements and the flagellate, *Trichomonas vaginalis*, and during investigations in this direction, a new medium for the isolation and propagation of *Trichomonas vaginalis* has been developed and reported.⁷ Since methods used in diagnosing 58 clinical cases for research studies have been sufficiently successful, it seemed desirable to make our procedures available to other workers in the field. This report deals with a clinical and laboratory approach to the problem, using a cultural method as a routine aid for the diagnosis of trichomonad infestations.

Material and Methods

The area surrounding the genitals is cleansed carefully by washing with green soap solution followed by distilled water. A sterile vaginal speculum, preferably unlubricated, is introduced, exposing the lower genital tract. The condition of the labia, vaginal mucosa, and cervix is noted as well as the character, color, odor, and amount of discharge present. Specimens for examination are drawn on cotton-tipped applicator swabs which are passed beyond the speculum blades, care being exercised not to touch the blades upon withdrawal of the swabs. The material is distributed directly to slides for wet-mounts, Gram's and iron-hematoxylin stained preparations, also to culture tubes containing 8 to 10 ml. of flagellate isolation medium (F.I.M.).⁷

The wet-mount is prepared by emulsifying a drop of the vaginal discharge in a drop of normal saline placed in the center of a glass slide which previously has been heated so that it is comfortably warm when touched to the back of the hand. The emulsion is mixed thoroughly with a wooden applicator stick or bacterial wire loop. A coverslip is placed at an angle to the slide with one edge

Summary

1. A total of 783 pregnancies of 500 consecutive multigravidas, gravida vi and over, are analyzed.
2. One-fourth of these are private patients.
3. Maternal morbidity is increased, necessitating an average increased hospitalization of 2.4 days per patient.
4. The maternal mortality rate is seven times that of the average mortality rate.
5. Fetal mortality is high in the multigravida, and the morbidity cannot be estimated.
6. Toxemias in the grandipara are increased over the average expectancy.
7. The frequency of placenta previa and premature separation is greater in the multigravida.
8. Malpresentations increase maternal and fetal mortality.
9. False labors are common in the multigravida.
10. Infections are prominent as causes of morbidity in the multigravida in pregnancy, labor, and the puerperium.
11. Medical complications other than those summarized above, which require treatment, are found frequently.

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culture tube. An alternative procedure involves the preparation of tubes containing the medium with a specimen swab wound directly into the cotton plugging the test tube. When collecting the specimens, this swab is moistened with the medium and passed through the speculum. After the discharge material has been collected on it, the swab is replaced directly in the tube of medium. Using either procedure, the culture is incubated after thoroughly mixing the specimen with the fluid medium. Incubation is maintained at 37 to 37.5° C. for 24 hours, after which time a drop of the sediment at the bottom of the medium is removed with a wide-mouthed bulb-type pipette. This is made up as a wet-mount, and is examined for trichomonads as was done with the original material. If trichomonads are not observed, the tube is returned to the incubator for an additional 24 hours. Following the second incubation period, the tube is gently shaken and rotated to mix all of the sediment with the fluid medium, and the entire contents are transferred to a 15 ml. centrifuge tube. After centrifugation at 1,200 r.p.m. for 15 minutes, the supernatant liquid is poured off, and the entire sediment mounted on a slide for examination as before.

The following two cases exemplify the use of the cultural method.

Report of Cases

CASE F-48.—Aged 41 years, married. The patient entered the office complaining of a recurrent trichomonad vaginitis which had been diagnosed by Dr. A., who believed that the urinary tract was the source of reinfection. A general physical examination revealed little of interest. Examination of the genitals showed a deep vagina exuding a profuse mucopurulent discharge. The cervix was large, firm, movable, and contained no masses. Urethral strippings showed no trichomonads in a wet-mount; however, smears from the vaginal discharge revealed an occasional trichomonad. Catheterized bladder urine had a specific gravity of 1.011, pH 5.6, and contained no albumin or sugar. Microscopic examination revealed an occasional white blood cell per high-power field, no red blood cells or casts, and a few epithelial plates in the sediment. No trichomonads were noted, and a Gram-stained mount revealed no bacteria.

A careful study of the bladder at this time revealed a diffuse injection of the entire area. The ureteral orifices readily admitted No. 4 ureteral catheters. Specimens of urine collected through these ureteral catheters revealed no trichomonads or bacteria. The patient was instructed to return for a morning urine examination. The total specimen of 430 ml. urine was distributed to tubes and centrifuged at 1,200 r.p.m. for 15 minutes. Carefully studied wet-mounts of the sediment revealed no trichomonads. The pooled sediments were distributed to four tubes of F.I.M.-hydrolysate medium which were incubated at 37.5° C. Duplicate plates of Sabouraud's dextrose agar were streaked; one incubated at room temperature, the other at 37.5° C. After one week of incubation, neither Sabouraud plate revealed evidence of mycological elements. The cultured morning urine specimen showed myriads of trichomonads after forty-eight hours.

To eliminate another possible source of infection, the patient's husband was examined. Physical findings were essentially negative. A urine specimen (No. 2 in "three glass test") had a specific gravity of 1.018, pH 5.2, and no albumin or sugar. Microscopic examination of the centrifugalized sediment revealed a rare white blood cell per high-power field, an occasional epithelial cell and no trichomonads. A Gram-stain showed no bacteria.

CASE LR-8.—Aged 34 years, married. Mrs. R. complained of constant pain in the urethra not associated with burning or frequency, and soreness in both costovertebral angles. A general physical examination was negative. Pelvic examination revealed a normal clitoris, urethra, and vagina. The cervix was badly lacerated. Catheterized bladder urine had a specific gravity of 1.010, pH 4.8, no albumin or sugar, and microscopically showed 5 to 7 white blood cells per high-power field, one red blood cell per high-power field, mucus and

near the drop but not quite touching it. The coverslip is then pushed along the surface of the slide until the edge contacts the drop allowing a small portion of the material to spread along the edge. The coverslip is finally allowed to drop upon the slide, drawing the fluid portion of the drop beneath the coverslip by capillary attraction thus excluding gross particles in the specimen. This method has provided satisfactorily thin and even preparations in all cases. Microscopic examination is made using the low and high dry objectives, with the substage diaphragm almost closed.

One drop of a 0.10 per cent solution of safranin in normal saline placed along the edge of the coverslip on the mount is drawn into the fluid portion under examination and provides a contrasting field for observation. We have found this concentration of dye nontoxic to the flagellates in wet-mounts over the period of time usually required for microscopic examination.

A smear is prepared for Gram's stain by emulsifying another drop of material in a drop of normal saline, and spreading the mixture evenly over two-thirds of the surface of a clean slide using a bacterial wire loop. Drying and fixing of the smear are accomplished in the usual manner. The Hucker modification⁵ of the Gram's stain has given us consistently good results and makes possible the recording, for research data, of the type of bacterial flora present, according to the modified classification of Loeser,⁸ as follows:

Type I: Gram-positive vaginal bacilli only.

Type II: Gram-positive vaginal bacilli plus mixed organisms including coccobacilli, diplococci, variable commas, streptococci, etc., and,

Type III: No Gram-positive vaginal bacilli, with disappearance of the variable commas and a predominance of cocci of all varieties.

The Gram-stained smear also serves to exclude gonococcal infections. It is routinely followed by culture on chocolate agar. Growths are confirmed by the oxydase test and fermentation subcultures.

Stained mounts are made and reserved for investigation if flagellates are not found in the wet-mount, and for examination while cultures are undergoing incubation. Faust's⁴ iron-hematoxylin staining method is used, preceded by wet-fixation in Schaudinn's sublimate solution.

Until recently, culturing of vaginal discharges for trichomonads has been inconvenient since a practical medium adequately supporting their growth and permitting reproduction in a short period of time has not been available. Numerous simple media designed for the propagation of routine laboratory stock strains (e.g., Cleveland-Collier liver infusion medium,³ Boeck and Drbohlav Locke egg serum medium²) have not been found sufficiently nutritive for rapid cultivation, and consequently have been inadequate as a laboratory diagnostic aid. A more desirable medium must contain necessary growth factors, be easily prepared, and must be capable of supporting growth and reproduction of flagellates from a minute inoculum containing very few flagellates.

Such a medium has been devised for the primary isolation of trichomonads from vaginal discharges and has been used in our laboratories for over one year. Although some authors have reported that trichomonads have never been found in cultures made from material diagnosed as "negative" by wet-mount (Stein and Cope,¹⁰ Bland et al.¹), we have diagnosed seven such "negative" wet-mounts as confirmed "positive" clinical cases after suitable culture of the material.

The medium, described in a previous communication,⁷ consists of a 2:3 serum-Ringer's solution with an equal part of a 1 per cent solution of an enzymatic yeast protein hydrolysate ("Prominogen") containing added agar, carbohydrates, and liver extract. The following procedure is used:

A sterile swab carrying a small quantity of the discharge material is placed in 10 ml. of F.I.M.-hydrolysate medium⁷ contained in a plugged 20 by 150 mm.

OVARIAN TUMORS AND UTERINE BLEEDING*

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IT HAS been assumed that some hormone-producing tumors of the ovary cause abnormal uterine bleeding, and it is widely accepted that nonhormone producing tumors may occasionally have the same effect. Since there have been few adequate attempts to explain the exact relation of these latter tumors to abnormal uterine bleeding, our original objective was to determine the nature of this relationship. As will be demonstrated, this objective was not attained. In fact, it was found that abnormal bleeding was not common, and when present was, in most instances, due to demonstrable intrauterine pathology, and not to the ovarian tumor.

Literature

Koucky,⁹ Mayer,¹² Lippert,¹⁰ Fauvet,⁶ Moulonguet-Dolérès,¹⁴ Marwil,¹¹ and many others have reported instances of menstrual irregularity as "due" to ovarian tumors (dermoids, Brenner tumors, serous and pseudomucinous cystadenomas, and ovarian carcinomas). Meyer¹³ suggested that abnormal bleeding might result from a metabolic upset in the ovary caused by the tumor growth. Moulonguet-Dolérès postulated that the tumors disturbed the nerve supply of the ovary, thus interfering with its function and secondarily effecting endometrial changes.

According to Berkeley, White, and Cook,² ovarian tumors may cause postmenopausal bleeding and menstrual abnormalities. Bourne and Williams³ agree, particularly insofar as postmenopausal bleeding is concerned.

Geist⁷ reported abnormal bleeding in over 40 per cent of 1,096 ovarian neoplasms of all types. His explanation was that "complicating local physical factors associated with uterine displacement and congestion are usually responsible."

Te Linde¹⁹ studied the general subject of postmenopausal bleeding; his series included 349 patients. He apparently believed that the bleeding was caused by benign nonhormonal tumors in eight. An additional eight malignant neoplasms were associated with bleeding but there was carcinoma in the uterus of five of them.

In a similar study of 406 postmenopausal bleeders, Taylor and Millen¹⁸ noted 23 instances of bleeding associated with ovarian neoplasms. However, intrauterine pathology was found in all but nine. Four of the latter were granulosa-cell tumors, and of the remaining five nonhormonal tumors, the uterus was not available in at least one.

In a study of the postmenopausal endometrium, Novak and Richardson¹⁵ concluded that with the exception of known hormone-producing ovarian tumors, ovarian neoplasms do not affect the endometrium; their occasional association with endometrial hyperplasia is probably a coincidence.

Several authors have granted that these tumors may be associated with abnormal bleeding, but have suggested that the bleeding was due to an unrecognized granulosa-cell tumor, or possibly a misinterpreted functioning neoplasm.

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an occasional squamous epithelial cell. A Gram-stained mount of the sediment revealed some Gram-positive cocci. A wet-mount and iron-hematoxylin stained smear of the vaginal discharge were negative for trichomonads.

An upper urinary tract study revealed normal renal pelves and ureters on both sides. Cultures of ureterally catheterized urine revealed Gram-positive cocci in abundance but no trichomonads were observed.

Twelve days later, the patient returned complaining of a vaginal discharge. Hanging-drop preparations made at this time were carefully examined by two independent observers and revealed no trichomonads, but swabbings of the vaginal and cervical secretions cultured in F.I.M.-Hydrolysate medium as described revealed many flagellates following incubation at 37.5° C. for forty-eight hours.

Material obtained from the cervix was plated to Sabouraud's dextrose agar and examination after one week at room temperature revealed numerous pasty, spready, white, sour-smelling colonies closely resembling *Monilia*. Subcultures and confirmation tests (fermentations, differential media, etc.) readily identified the organism as *Monilia albicans*.

Of interest is the fact that with successful treatment of the monilial infection, the vaginal trichomonad infestation also disappeared, but recurred intermittently for a period of five months. On three occasions, although no trichomonads were noted in the wet-mount, they were recoverable upon culture of the material.

Summary

By usual laboratory methods, 51 cases of trichomonad vaginitis in 58 studies were diagnosed. The use of a yeast protein hydrolysate-enriched medium permitted the remaining so-called "negative" cases to be culturally diagnosed as "positive" *Trichomonas vaginalis* infestations. A systematic laboratory protocol has been outlined, and the use of a cultural method is discussed and advocated as an aid in diagnosis. Two typical case reports are presented.

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the hospital she had spotted for seven days. At operation, a cystadenocarcinoma was removed along with the uterus. Microscopic preparations of the uterus showed atrophic endometrium with an occasional gland and areas of necrosis covered with fibrin and infiltrated with inflammatory cells. Pyknotic stromal nuclei and other degenerative changes were seen. The bleeding was judged to be due to the intrauterine pathology and not to the ovarian tumor.

CASE 4.—The patient was 59 years old and was 18 years postmenopausal. During the two months prior to admission she bled a small amount at irregular intervals. A papillary serous cystadenoma was removed with the uterus. The endometrium was atrophic but had areas resembling the estrogenic phase of the childbearing period. Such a picture is, of course, not unusual in the postmenopausal period (Novak and Richardson,¹⁵ and Fahlund and Broders⁵). A small fibroid 1.5 cm. in diameter was located just below the endometrium. Unfortunately the gross tissue was not available, and judging from multiple sections, the block had been cut to include only the edge of the tumor. No probable source for the bleeding was found in the available sections, and its cause was not determined.

Premenopausal Group

This group included 47 patients with ovarian tumors. Eleven (28 per cent) of these patients had had abnormally excessive, prolonged, or irregular uterine bleeding. The cause was obvious intrauterine pathology in six patients (endometrial polyps in four; uterine carcinoma in one; submucous fibroid in one). The five remaining cases are described.

CASE 5.—A 37-year-old woman whose history was much too brief, merely a statement that she had had "functional uterine bleeding" prior to surgery. The ovarian tumor was a pseudomucinous cystadenoma. A recent corpus luteum was noted. The endometrium was secretory. Our information on the patient is too scant to make satisfactory evaluation possible.

CASE 6.—The patient was 23 years old. Seven years before, following childbirth, she developed pelvic inflammatory disease. Since that time she had had uterine bleeding every 10 to 15 days for 7 to 10 days. Microscopic examination revealed a serous cystadenoma and residues of pelvic infection. The endometrium was in the proliferative phase but also showed evidence of chronic infection. The onset of the abnormal bleeding immediately following the onset of the pelvic inflammatory disease and the operative findings of the residues of the disease would implicate them as the cause of the bleeding. Though we know of no satisfactory explanation as to the exact mechanism, it is a known clinical fact that abnormal uterine bleeding may be found with residues of pelvic inflammatory disease.

CASE 7.—Following a blow to her abdomen twelve years before, a 37-year-old woman was operated upon. Some unknown ovarian surgery was performed. No tumor was noted but following the operation she bled every 10 to 15 days for 3 to 5 days. The endometrium was in the secretory phase, with no pathology noted. The ovarian tumor was a serous cystadenoma. The bleeding pre-existed the tumor in this patient. It, therefore, seems obvious that the tumor did not cause the bleeding.

CASE 8.—The patient was a 37-year-old woman whose only menstrual irregularity was regular midcycle spotting for 4 to 5 days during the past year. The ovarian tumor was a dermoid. The endometrium was secretory. This apparently represents the not too rare phenomenon of midcycle spotting associated with ovulation. To attribute the cyclic spotting to the dermoid hardly seems justified.

CASE 9.—A 24-year-old woman with an ovarian fibromyoma, who for the past year had menstruated every 21 days instead of her usual 28, with a two-day flow instead of five. Midcycle spotting was an occasional occurrence. It was noted on her history that the last menstrual period was 26 days previously. The endometrium was in the secretory

The latter suggestion is R. Meyer's¹³; the former, G. van S. Smith's.¹⁷ Unless we misinterpret them, both Payne,¹⁶ and Bourne and Williams³ infer that these tumors may have unrecognized ability to produce hormones. With this in mind, Adair and Watts¹ investigated the hormone content of ovarian cyst fluids and found "no results which warrant conclusions."

Material

Tissues were available from 154 patients with cystic or solid nonhormone-producing ovarian tumors. For the purpose of this study it was necessary also to have access to the uterine tissues. Since many of these tumors were benign and from relatively young women, hysterectomy had not always been done; consequently, only 74 tumors with accompanying uteri were available. Although this is admittedly a small group, if the original thesis is true, viz., that ovarian tumors may cause irregular uterine bleeding, supporting evidence should appear in a series of this size.

The microscopic sections, gross pathology reports, and the clinical charts were studied in detail. The number of each type of tumor is given in the table.

TABLE I

Pseudomucinous cystadenomas		9
With area resembling serous cystadenoma	2	
With accompanying fibroma	1	
With Brenner tumor	1	
Serous cystadenomas		18
With accompanying fibroma	1	
Serous cystomas		5
With accompanying dermoid	1	
Dermoids		17
Fibroma and fibroadenoma		7
Carcinoma		18

Twenty-seven of the tumors were removed from postmenopausal women. For the purposes of this study a woman was not considered postmenopausal until at least a year had intervened since her last menstrual period. The remaining 47 were considered to be premenopausal although 32 of them were forty years of age.

Findings, Postmenopausal Group

Only four of the 27 patients in this group had postmenopausal bleeding. In two of these patients the bleeding was obviously not due to the tumor per se but to intrauterine pathology. In the third patient, hemorrhagic areas in a hyperplastic endometrium caused bleeding. In the fourth patient, the cause of bleeding could not be definitely determined.

CASE 1.—Was four years postmenopausal. She had a serous cystadenoma, but her bleeding was due to superficial areas of hemorrhagic necrosis in hyperplastic endometrium. The latter as judged by her history was due to the injudicious administration of estrogens during the preceding three years.

CASE 2.—Was 15 years postmenopausal and complained of bleeding for two weeks. Tissue examination revealed a cystadenocarcinoma with metastases to the myometrium. Though serial sections of the small amount of tissue available were searched, no endometrial involvement was demonstrable. A marked hyperplasia present, with numerous hemorrhagic areas was the cause of the bleeding.

CASE 3.—Was a 52-year-old woman who had had no bleeding for seven years following dilatation and curettage and radium for functional bleeding. Prior to admission to

It seems likely that these three specimens actually represent instances of reawakening of ovarian activity. Indicative evidence of similar occurrences has been presented by other workers. Cheek and Davis⁴ noted secretory endometrium in a woman two years postmenopausal, who had had an episode of bleeding, and no palpable ovarian tumor. Fahlund and Broders noted the presence of a corpus luteum in the ovary of a 63-year-old woman who was 25 years postmenopausal.

Summary and Conclusions

A possible relation between abnormal uterine bleeding and nonhormone-producing ovarian tumors was investigated. Tissues that included uteri as well as the ovarian tumor were available from 74 patients. Abnormal uterine bleeding was not common and in all but three instances definitely could be attributed to causes other than the ovarian tumor. It seems unlikely that nonhormone-producing ovarian tumors, per se, cause abnormal uterine bleeding.

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phase. It seems rather questionable that we should classify this as abnormal menstruation. One wonders about the accuracy of the history in view of the stated last menstrual interval.

Comment

In 74 pre- and postmenopausal patients fifteen (20 per cent) had abnormal bleeding. In all but three of these patients (Cases 2, 4, and 5) other factors than the ovarian tumor were found which could well explain the bleeding. In one of the three the history was unsatisfactory, merely a statement that the patient had "functional uterine bleeding."

In this study we were not able to find any relationship between the tumors and the endometrial picture. It seems likely that the nonhormonal ovarian neoplasms per se, rarely, if ever, cause abnormal uterine bleeding; furthermore, if adequate study of the pertinent material is done another cause will be found in almost all instances.

Additional Data

The variability in the status of the postmenopausal endometrium was of interest. Less than half (44.4 per cent) showed atrophic endometrium—thin endometrium with scanty glands and low, inactive-appearing epithelium. Approximately a quarter (25.9 per cent) of the endometria had areas of atrophy intermingled with areas where the glands were greater in number, well developed and with high epithelium—areas that resembled the estrogenic phase of a normally cyclic uterus. Two other patients (7.4 per cent) had endometria identical in all respects to that of the normal proliferative phase. The remaining 22 per cent had hyperplastic endometria (excluding the one caused by administered estrogen) but only one of them had been bleeding.

Thus, according to commonly accepted criteria, over half of these postmenopausal women had endometria that showed evidence of estrogenic stimulation. These findings, of course, are not new. Essentially similar findings have been reported by Novak and Richardson, and by Fahlund and Broders.

In none of these postmenopausal patients was there histologic evidence of functional ovarian activity to account for the estrogenic stimulation of the endometrium. In another patient, excluded from this series, such evidence was found. This 46-year-old woman was two years postmenopausal and had had uterine bleeding for five months. The original pathologic diagnosis on her tissues was serous cystoma. Actually, the cyst was a regressing atretic follicle cyst and for this reason she was excluded from this series. Her endometrium was identical to that of the late proliferative phase. Sections of ovarian tissue included a completely normal mature follicle in addition to several small atretic follicles. In this particular instance, the patient had been judged to be postmenopausal because of her history. Actually, judging by the appearance of the ovaries, she had continued to have ovarian activity in spite of the absence of menses.

The findings in this patient cannot be interpreted as support for the theory that on rare occasions postmenopausal uterine bleeding may be caused by a temporary reawakening of ovarian activity. However, this does occur. We have studied the tissues from three such cases. Each of the three patients was at least two years postmenopausal and complaining of uterine bleeding. In each, the ovaries were small, shrunken, inactive, and typical of senile ovaries. In each, however, there was a partially collapsed cystic structure with a wall composed of layers of partially or completely luteinized granulosa and theca cells. The endometria of these patients were hyperplastic and had superficial areas of hemorrhagic necrosis.

canal at the level of its middle third. The origin of its upper extremity could not be determined definitely. There was a profuse yellowish discharge bathing the cervix and vulva. The perineum was found reddened, excoriated in several points, and tender to the touch. The appearance of it gave credence to the patient's statement that the leucorrhea was of long standing. When this strip of membrane was gently touched, slight bleeding occurred, which was easily controlled by pressure. A piece of tissue, measuring 1.5 cm. in length was removed and fixed in 95 per cent alcohol for future study. Grossly, the strip of tissue appeared paper thin, firm, and resembled fetal membranes. After removal of this tissue, another small piece was still visible in the cervical canal. At the second prenatal visit, three days later, it was still present in the upper portion of the cervix. During the following two weeks the patient, according to her statement, was passing small bits of tissue in addition to the fluid vaginal discharge. At the end of this period the author observed the membrane in the patient's cervix for the last time.

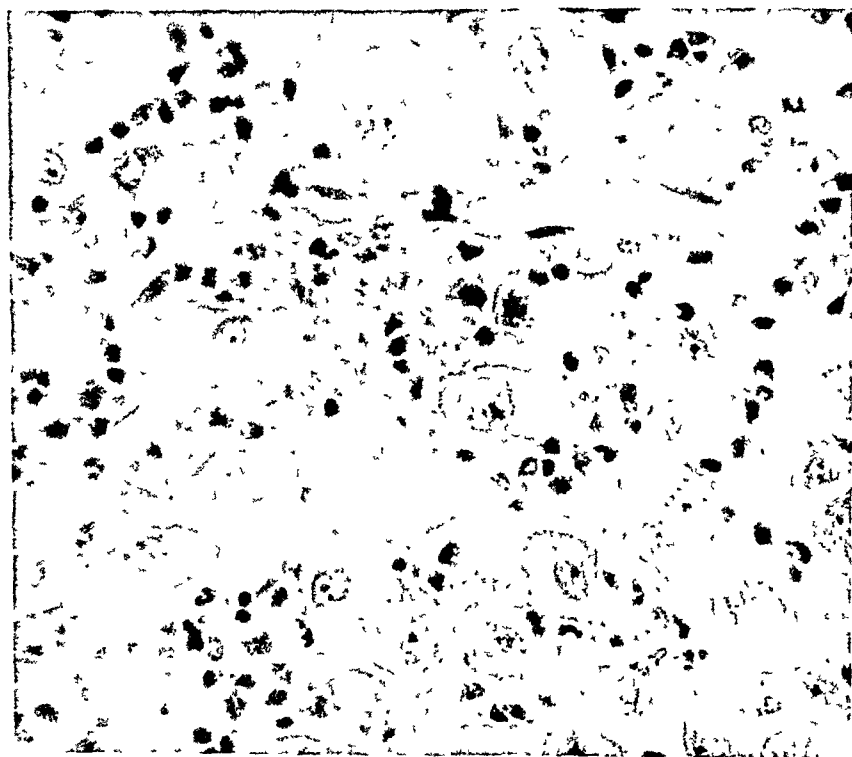


Fig. 1.—Microphotograph of the decidua. This field shows decidua cells with their characteristic vesicular nuclei. The mosaic pattern of the polygonal cells, some of which contain vacuoles, is well illustrated and so is the presence of some caudate forms. Note the large number of polymorphonuclear leucocytes, widely disseminated between the decidua cells. A thin-walled blood vessel is seen in the upper third of the picture. H and E stain, $\times 400$.

The patient complained that on several occasions she had seen small streaks of blood in her vaginal discharge. The bleeding occurred mostly upon exertion, urination, or defecation. The spotting of blood ceased at 7½ months of her pregnancy. The profuse leucorrhea continued throughout its entire period, save for the week just preceding the delivery. The prenatal course was uneventful in every other respect. The blood pressure readings and repeated urinalyses were normal throughout the whole period of gestation. The weight gain and blood count were within normal range. The Kahn test was negative and the patient was free from Neisserian infection. Her blood belonged to group A and was Rh negative, with no antibodies present. Her husband, fortunately, was Rh negative also. The rabbit test (Friedman) was positive for pregnancy.

On July 29, 1947, one week before term, the patient was admitted to the Mount Sinai Hospital in active labor. After a first stage of six and one-half hours and second stage of

SHEDDING OF DECIDUA DURING UTERINE PREGNANCY AND ITS CLINICAL SIGNIFICANCE

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DURING pregnancy the uterine mucosa undergoes characteristic changes which are known as decidual reaction. At one time, the decidual transformation was considered the histologic characteristic of the endometrium alone. With the accumulated knowledge it was learned that decidual tissue may be found not only in the endometrium but in the cervix also. Bayer¹ is being credited with the first (1885) demonstration of decidual tissue in the cervix. A number of publications appeared in the literature since then. Some authors described localized elevations or nodules upon the portio vaginalis uteri. Others saw this tissue within the cervical canal or at the external os, appearing as polyps or tumorlike structures. Still others found decidual cells in the cervical erosions. Most of the writers considered their findings unusually rare. While in some cases the occurrence of decidual tissue in the uterine cervix may have only an academic interest, in others it is associated with a symptomatology which might confuse the diagnosis and alter the prognosis of the pregnancy, unless the true nature of the lesion be recognized. The present author's case, which differed essentially from others, emphasizes this point clearly. The tissue in question, found in the cervical canal of an early pregnancy, resembled grossly fetal membranes. This finding aroused fear for the pregnancy itself and raised the question of proper treatment. To emphasize the diagnostic pitfalls and their avoidance is the purpose of this report and its justification.

On Jan. 16, 1947, Mrs. M. L., a 31-year-old white woman presented herself with a history of amenorrhea of ten weeks' duration. Her last menstrual period occurred on Oct. 28, 1946. She complained of a profuse vaginal discharge of long duration, which became especially aggravated during this period of amenorrhea. The discharge was very annoying and irritating, causing rawness and soreness of the perineum.

Her past history revealed a number of childhood diseases. Diphtheria, whooping cough, measles, and mumps were among those she could remember. Her menses began at the age of 14 years. The periods occurred regularly; the flow, moderate in amount, lasted four to five days. There was no history of dysmenorrhea, clots, or other abnormalities. Her past obstetric history revealed that in 1943, after a protracted labor, the patient was delivered of a living child by a midforceps operation. The recovery from the delivery was uneventful. However, the patient dates the onset of the vaginal discharge from the birth of her child. Her family history was negative and irrelevant to the present condition.

The general physical examination of this well-nourished woman was essentially negative except for a systolic murmur at the apex of the heart. A slight contraction of the transverse diameter of the outlet, which measured 9 cm., was the only deviation from normalcy in the pelvic measurements. The pelvic examination disclosed a soft, movable, anteverted uterus, enlarged to the size of about 10 weeks' gestation. The adnexa were not palpable. The cervix was inflamed and badly eroded. A grayish-white membrane was visible within the cervical

one hour, fifty-four minutes, the patient was delivered by low forceps of a normal living child in good condition. The placenta was delivered by early expression after a third stage of four minutes; the loss of blood was estimated at 200 c.c. Careful inspection revealed no abnormalities in the placenta or membranes, which were of usual thickness and smoothness. The puerperium ran an uneventful course, the lochia appeared normal and contained no unusual tissues. There was no morbidity, according to the accepted standards, the highest temperature being 100.2° F. on the evening of the date of delivery. The uterus was involuting satisfactorily. Postnatal examination, at two months post partum, revealed an inflamed and eroded cervix and a well-involuted uterus. The adnexa were not palpable. The vaginal discharge, although diminished in quantity, was profuse still. The pelvic floor was found moderately relaxed and the perineum excoriated still in a few areas.

Microscopic Study of the Specimen.—The major portion of the section consists of decidual cells. These are large, polygonal cells, which vary widely in size. Besides the polygonal, spindle-shaped and caudate forms are seen. The cytoplasm is finely granular and displays vacuoles frequently. The nucleus is vesicular, large, excentrically located and contains coarse granules. Occasionally two nuclei were found in one cell. In some fields the typical mosaic pattern can be observed (Fig. 1), in others edema can be detected. Polymorphonuclear leucocytes are widely disseminated between the decidual cells, in some areas crowding them out completely. In several areas foci of polymorphonuclear leucocytes predominate the field, where they are present almost to the exclusion of any other tissue (Fig. 2). The whole specimen is richly supplied with thin-walled blood vessels of various diameters. There is one large area of necrosis where only shadows of decidual cells can be recognized and few blood vessels detected. Even here leucocytes can be found in large numbers and well stained (Fig. 3). It should be emphasized that the inflammatory infiltration is a striking feature of the microscopic picture.

Discussion

Decidual reaction in the cervix during pregnancy is not nearly as rare as was formerly believed. Decidual or decidua-like cells were repeatedly seen in the cervical stroma by several observers under normal and abnormal conditions (Hofbauer,⁸ Novak,¹⁶ Kramann¹⁰). That decidual reaction to a limited degree does normally occur in the cervical mucosa is accepted by Greenhill in DeLee-Greenhill's⁴ "Principles and Practice of Obstetrics." Stander,²⁰ too, mentions the rare occurrence of isolated decidual cells underneath the cervical epithelium. Since Bayer's¹ publication in 1885, a number of articles were added to the literature. Most of the authors described tumorlike formations within the cervical canal or upon the portio vaginalis. Frequently decidual tissue was found in association with cervical erosions and polyps. Lynch¹³ in 1913 collected from the literature twenty-two cases of localized decidual growths in the cervix and added one of his own. Willer,²¹ in 1935, assembled seventeen cases of decidual cervical polyps, two of his cases being included in the series. The last decade brought a number of papers upon this subject. Thus, cases were reported by Ostrčil,¹⁷ v. Latzka,¹¹ Willer,²² Göbel,³ Kramann,¹⁰ Hennessy,⁶ Klein and Domeier,⁹ and Haas.⁵ When decidual tissue, well localized and circumscribed, is found either upon the portio or within the two lower thirds of the cervical canal it can be classified as ectopic decidua, since its origin from the endometrium can be positively excluded. On the other hand, considerable more difficulty is encountered when the structure is located in the vicinity of the isthmus. To trace the origin of a tissue in this location is neither easy nor feasible. In the present author's case, the lower edge of the membrane was seen in the middle of the cervical canal. After 1.5 cm. of this tissue had been removed, some more of it was visible at a higher level. Further exploration was omitted for fear of producing hemorrhage difficult to control here, or of endangering the pregnancy. The tissue itself did not contain glands or surface epithelium, the presence of which could have helped in the differential diagnosis.

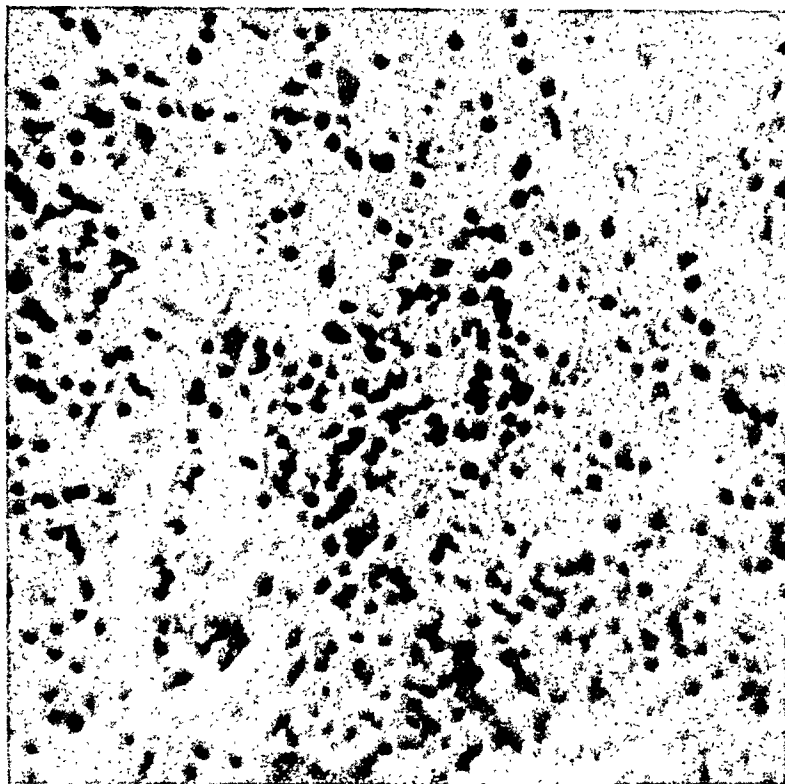


Fig. 2.—Another area of same specimen. This field shows foci of leucocytic infiltrations. Only an occasional decidual cell can be detected here and there. H and E stain, $\times 400$.

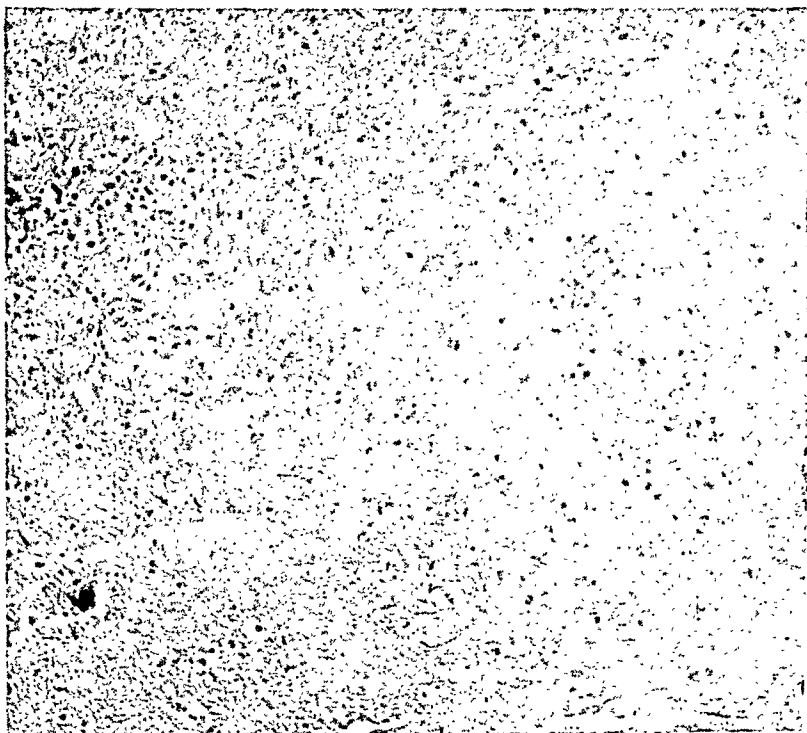


Fig. 3.—An area of necrosis, same specimen. The tissue here appears pale and poorly stained. The decidual cells lost their sharp outline, and they are difficult to recognize, only shadows of them are seen. The leucocytes are numerous even here and have retained to a considerable degree their staining properties. H and E stain, $\times 180$.

during pregnancy, are also known. Once the pathology of the lesion is understood, the problem of treatment becomes simplified. In most cases, the vaginal bleeding is mild and should cause no concern to the attending physician. However, should it be profuse, it can be controlled by pressure or excision or cauterization of the lesion, the pregnancy being left undisturbed. In those cases which had been subjected to biopsy, the healing was prompt and complete. A partial excision of the growth for purposes of study, strangely enough, caused permanent cessation of bleeding for the remainder of the pregnancy (Samuel¹⁹). An interesting point for speculation is the mechanism of bleeding in cases of cervical decidua. The mere presence of decidual cells, per se, cannot be the cause of it. The great vascularity of the lesion and the tendency to necrosis may furnish a plausible explanation. The removal of friable and necrotic tissue and its substitution by a healthy scar may be a satisfactory explanation for the observation that even biopsies have been able to check the bleeding permanently.

As mentioned already in the case presented here, the tissue, the lower end of which was found in the middle third of the cervical canal, resembled grossly a strip of fetal membranes. In this location, a membranous structure whose upper pole is ill defined can be confused easily with parts of the ovum itself. Its presence here may lead to an erroneous assumption that an abortion is in progress, though pains may be absent. An error like that may be costly to the pregnancy, if one interferes before the microscopic study has been completed. In the author's case, no such action was contemplated because the bleeding had been slight, and the time element was of no great moment. Should a similar macroscopic picture be associated with a more copious bleeding, then the temptation to interfere may be great. Even when the extruded tissue is known to be decidua, another stumbling block may be encountered, unless one is aware of such cases. It is generally accepted that extrauterine pregnancy is accompanied often, although not always, by decidual reaction in the endometrium. The passage of a decidual membrane may not only suggest this diagnosis but also the death of the embryo. A complete history, a careful pelvic examination, the proper interpretation of the Aschheim-Zondek test or any of its modifications, and a discerning evaluation of the symptomatology will be rewarded, in most cases, by a correct diagnosis.

What should the management of such cases be after the diagnosis has been made? In the author's belief, no special treatment is indicated, save for the control of bleeding, if present. This patient was not confined to bed and no special medication was given. At no time, since the nature of the tissue became known, was the pregnancy considered in danger. The patient was allowed her usual activities and continuation of her household duties. Sexual intercourse, however, was interdicted for fear of contact bleeding.

In conclusion, it can be said that if the source of every bleeding in pregnancy be determined, and if the histologic character of every tissue expelled be investigated, then some operative deliveries could be avoided on one hand and some pregnancies salvaged on the other. An accurate diagnosis and knowledge of the underlying pathology are essential for the intelligent management of such cases and indispensable for the acceptance of the old adage, *Primum—non nocere!*

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Histologically, the tissue was identical with the picture seen in the compact layer of decidua vera. Since the mucosa of the isthmus is considered as normally undergoing decidual reaction in pregnancy, decidual tissue in its close vicinity is difficult to classify as ectopic with certainty, unless the whole uterus is available for gross and microscopic study. The present author will refrain from positively identifying the decidua of her case as ectopic, although it may well be that. In the case presented here, the source of the decidua, interesting though it might be, is irrelevant to its clinical importance.

Normally, the endometrium undergoes decidual transformation during pregnancy, and quite naturally this phenomenon was ascribed to the action of the gestational hormones. Outside of pregnancy, decidual reaction of the stroma of the endometrium was observed at times, in cases of polycystic ovaries (v. Latzka¹¹), of corpus luteum cysts (Kramann¹⁰), in luteomas (Novak¹⁶), and in the premenstrual endometrium in which a deciduallike appearance was described (Novak,¹⁶ Curtis,² Reinhart,¹⁸ and others), ergo in conditions in which the secretion of corpus luteum hormone is augmented. From the results of his experiments on guinea pigs, Loeb¹² in 1908 postulated that the corpus luteum secretes a substance necessary for development of deciduomas in the animal's uterus, which underwent mechanical stimulation. His views have received wide acceptance and were, subsequently, corroborated by other workers in different species. Nelson and Pfiffner¹⁵ were among the first few to produce experimentally deciduomas in spayed rats by injections of extracts of the corpus luteum, which preceded and followed the mechanical irritation of the uteri. Since then, a number of investigators produced deciduomas in various species by using the progestational hormones in one or another form. These experimental data adduced presumptive support for the clinical chain of evidence which implicates the corpus luteum hormone in the process of decidual formation in man.

Ectopic decidua, by analogy, is also considered a product of corpus luteum hormone stimulation but of nonendometrial tissue. Since ectopic decidua is not a regular finding in every pregnancy, some other factor besides hormonal, must be present for this reaction to occur. Many theories, into discussion of which the author does not intend to enter here, were propagated by various investigators. The theory of R. Meyer¹⁴ that the inflammation, so often accompanying ectopic decidua anywhere in the body, is the sensitizing agent that prepares the susceptible tissues for hormonal response, is of great interest. It seems that this point of view has found corroboration in the histologic picture of many cases of ectopic cervical decidua. In most cases, leucocytic and lymphocytic infiltrations were observed with frequency, almost regularity. In the case presented here, foci of polymorphonuclear leucocytes were a prominent feature of the histologic picture. Even grossly, the cervix appeared inflamed, badly eroded, and exuding a profuse, mucopurulent discharge.

The importance of localized decidual growths, found in the cervix, whether ectopic or not, does not lie in their rarity, but in the fact that their presence might be confused with other, more serious, lesions of the cervix. When located upon the portio or within the cervical canal, these lesions have been mistaken for cancer, tuberculous ulcer, or syphilis. Hinselmann⁷ himself failed to make a correct differential diagnosis even with the aid of the colposcope. Careful microscopic studies have been necessary before a correct diagnosis was made in his case. Another point of practical importance is that decidual formations in the cervix may be associated with vaginal bleeding. This bleeding is usually mild but may be profuse and may lead to a faulty diagnosis of placenta previa. Such mistakes have known to occur (Klein and Domeier⁹) and can be prevented by a careful pelvic examination and especially by the use of the vaginal speculum. Cases of bleeding from cervical erosions and polyps, undergoing decidual reaction

A STUDY OF 145 CONSECUTIVE TWIN PREGNANCIES

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THIS paper represents a study of 145 consecutive sets of twins delivered in the twelve-year period from 1935 to 1947 at the St. Louis City Hospital. During this time there were 15,878 deliveries. The incidence of twinning was 0.91 per cent, or about 1 in 103 deliveries. All of the mothers were white. Das,¹ in his demographic study of twins, showed the incidence among the whites in the United States to be about 1 in 88. This figure is paralleled by Guttmacher,² Gernez and Omez,³ Potter and Crunden⁴ and Silbenthal.⁵

Many investigators have already reported the frequency of multiple pregnancy among the multiparas. Only 20 per cent of the twin deliveries in our series occurred among primiparous women. There were 19 sets of identical twins delivered in this study, an incidence of 13.1 per cent. Fraternal twins numbered 126 sets, or 86.9 per cent. Guttmacher² noted in his study an incidence of fraternal twins of 93.3 per cent. One hundred fifty, or 51 per cent of the newborn were female. Both sexes were represented in 52 sets, or 35.8 per cent. The sex ratio varied but slightly from the normal expectation.

Prenatal clinics were attended by a minority of the mothers. The burden of multiple pregnancy definitely increased the incidence of toxemia. Twenty-nine and six-tenths per cent of the pregnancies were complicated by a toxemia. Of these 43 cases of toxemia, there were four cases of eclampsia. Polyhydramnios was noted in six of the pregnancies.

The diagnosis of twin pregnancy depends largely upon the size of the babies. The average weight of the twins in this study was 2,420 Gm., with the largest set having a combined weight of 8,060 Gm., or 17 pounds, 12 ounces. Park⁶ recently reported a set of twins whose combined birth weight was 19 pounds, 2 ounces.

Other factors, such as obesity, the stage of labor, and the duration of the pregnancy, play an important role in the facility of diagnosis. The diagnosis is not simple, but when suspected can be confirmed by the use of the x-ray. In this series, most of the mothers entered the hospital in active labor. The weights of the babies were fairly equally distributed in three groups. The greatest accuracy in diagnosis was noted in those groups where at least one or both of the babies weighed over 2,500 Gm. The poorest diagnostic ability was demonstrated in the group where both babies weighed less than 2,500 Gm. each. Table I classifies this series according to birth weight and accuracy of diagnosis.

All but two of the deliveries in our study fell in the four common groups of presentation. The incidence of the presentations was roughly identical with the figures usually found by other authors. Table II compares the presentations in this group with that of Leonhardt.⁷

Concern about delivery is due chiefly to the delay incident to uterine inertia, and to a complication known as collision; the latter is exceptionally

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corrected premature fetal mortality rate was 26.6 per cent, and the corrected full-term fetal mortality rate was 3.2 per cent. This represents a definite increase in the mortality rate for twins as compared to the general obstetric service where the full-term mortality rate was only 1.21 per cent. Table III presents infant mortality and maturity comparisons.

Operative interference was noted to have a corrected mortality rate of 10 per cent. Though this is high, the policy of teaching the technique of versions utilizing the second twin should not be abandoned, for the corrected death rate for that procedure was only 3.47 per cent. The high forceps death rate was due mainly to difficult forceps rotations. Table IV illustrates the

TABLE IV. INFANT MORTALITY AND OPERATIVE INTERFERENCE

OPERATION	CASES	MACERATED STILLBORN	STILL- BORN	NEO- NATAL DEATH	POSTNEO- NATAL DEATH	TOTAL DEATHS	CORRECTED DEATH RATE PER CENT
Versions and extractions	29	1	1	1	1	4	3.4
Forceps and episiotomies	21	2	0	4	2	8	19.0
Total	50	3	1	5	3	12	10.0

mortality rates in those cases in which operative interference was noted.

Among the complications of delivery, the cord was wrapped around the neck of the infant in nine cases. Three prolapsed cords were noted.

The incidence of postpartum hemorrhage was definitely high in this study. Excess blood loss (more than 500 c.c.) occurred in thirteen cases. Hemorrhage caused the one maternal death for an incidence of 0.68 per cent, or 68 per 10,000. Hirst⁸ and others have pointed out that in twin pregnancies, maternal, neonatal, and stillbirth rates are roughly increased three times over those for single births. In one instance it was necessary to pack the uterus. In three cases of retained placenta, manual removal was necessary. The tendency toward postpartum hemorrhage is explained on the basis of uterine atony resulting from overdistention by the multiple pregnancy.

Perineal tears were infrequent. There were five first-degree, and seven second-degree tears. There were no third-degree tears. One cervical laceration requiring suture was encountered.

Placental malformations were particularly high. There were two circumvallate placentas and one velamentous insertion of the cord. There were three cases of marginal placenta previa, an incidence of 2.1 per cent. There was only one premature separation of the placenta. The increase in the size of the placenta probably accounts for the increase in the incidence of low-lying placentas.

Five fetal monstrosities were encountered.

Summary

1. A series of 145 consecutive twin deliveries at the St. Louis City Hospital occurring during the last twelve years was analyzed.
2. The incidence of twinning was about 1 in 103 deliveries.
3. In 80 per cent the mothers were multiparas.
4. The incidence of identical twinning was 13.1 per cent.
5. A toxemia complicated the pregnancy in 29.6 per cent.
6. The diagnosis of multiple pregnancy was not easy, especially when both babies weighed less than 2,500 Gm.
7. The presentations varied but little from those presented in the literature.

rare and was not encountered in this study. The fetal membranes of the second child usually appear at the cervix after the first child is born, and rupture soon follows. The delivery of the second child occurs within a short time of the delivery of the first. In the group under study, 90, or 62.7 per cent, of the second babies delivered within the first 15 minutes, and 123, or 84 per cent, were born within 30 minutes of the first baby; 98.6 per cent delivered within one hour. In only six cases did the birth of the second child occur over an hour after the first. The longest time interval between any two babies was two hours and fifty-three minutes.

Operative interference was frequent in this series. In delivery of the second child, 29 (20 per cent) versions and extractions were performed. There were 21 forceps and episiotomies and one manual rotation of an occiput posterior. Forceps rotation was done in four cases.

TABLE I. DIAGNOSIS AND BIRTH WEIGHT

BIRTH WEIGHT	CASES	PER CENT	DIAGNOSED	NOT DIAGNOSED	PER CENT DIAGNOSED
Both over 2,500 Gm.	56	38	35	21	62.5
Only one over 2,500 Gm.	40	27.5	18	22	45.0
Both under 2,500 Gm.	49	33.9	18	31	36.8
Total	145	100	71	74	49.0

TABLE II. PRESENTATION

PRESENTATION	CASES	INCIDENCE	LEONHARDT'S INCIDENCE
Vertex-vertex	73	49.9	38.5
Vertex-breech	38	26.1	21.2
Breech-vertex	20	13.8	14.4
Breech-breech	12	8.2	10.8
Breech-transverse	1	0.7	4.3
Transverse-vertex	1	0.7	0.8
Total	145	100.0	90.0

TABLE III. INFANT MORTALITY AND MATURITY

MATURITY	CASES	MACERATED STILLBORN	STILL-BORN	NEONATAL DEATH	POST-NEONATAL DEATH	TOTAL DEATHS	CORRECTED DEATH RATES PER CENT
Full-term	155	0	7	5	3	15	3.2
Premature	135	3	5	36	5	49	26.6
Totals	290	3	12	41	8	64	14.1

In the correction of the full-term mortality rates, elimination depends upon the presence of the following conditions:

1. Macerated stillbirths
2. Stillbirths in which fetal heart was not heard prior to labor
3. Postneonatal deaths (after two weeks)
4. Syphilis

In the correction of premature fetal mortality rates, the birth weight of 1,500 Gm. was arbitrarily chosen as the weight of viability.

Of the 148 sets of twins there were 135 premature and 155 full-term infants delivered. There were 15 full-term and 49 premature deaths. The

OBSERVATIONS IN BEHAVIOR OF PRESENTATION AND RESULTS WITH EXTERNAL VERSION IN 190 BREECH CASES*

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THIS paper will give evidence that 98.4 per cent of spontaneous changes in presentation occur before the thirty-fourth week of pregnancy, that the period between the thirty-second and thirty-fourth weeks is the best time for correcting faulty presentations, and that, for breech delivery, it is the footling type that is most hazardous.

The Kings Daughters Maternity Center in Norfolk, from which eighty-eight of these cases are taken, is an out-patient clinic, from which abnormal cases are referred to a hospital, and normal cases are delivered at home by senior students. The effort to avoid taking complicated cases for home delivery sharpens attention on prenatal diagnosis. From about the thirtieth week, patients are placed on the table at every visit, and presentation and position are recorded. Each is checked at least once by a consultant, and oftener when an abnormality is found. When we are in doubt about presentation, or disagree, x-ray films are ordered. Among these eighty-eight breech cases personally checked, only five were x-rayed.

That the diagnosis of presentation without x-ray may be erroneous is acknowledged. To check on this point one thousand clinic charts were personally examined, to see how the recorded prenatal diagnosis checked with the recorded presentation at delivery. These charts were unselected, except that each had to show the record of at least four prenatal examinations, and the record of presentation as delivered. They did not include the charts of known breech cases separately considered. Three incorrect diagnoses were found; three times I diagnosed "vertex," when it proved to be a breech. A fourth unexpected breech had not been checked by a consultant. So the percentage of error appeared reasonably satisfactory.

In the same one thousand charts, the instances of spontaneous change in presentation after the thirty-second week were also counted, with the following results:

Breech to vertex, or vertex to breech	32nd to 34th week	16
	34th to 36th week	2
	36th to 40th week	2
Transverse to upright	32nd to 34th week	0
	34th to 36th week	1
	36th to 40th week	2

Only seven changed after the thirty-fourth week, less than 1 per cent.

*Read at the Tenth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Augusta, Ga., Feb. 12 to 14, 1948.

8. Eighty-four per cent of the second infants were delivered within thirty minutes of the first.

9. Postpartum hemorrhage was encountered in 8.9 per cent of the deliveries and caused the single maternal death for a rate of 68 per 10,000.

10. The maternal, full-term, and premature mortality rates were elevated to about three times that of single pregnancies.

11. Operative interference, especially in the delivery of the second child, should not be abandoned.

12. Placenta previa occurs more frequently in multiple pregnancy.

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16 HAMPTON VILLAGE PLAZA

legs on upturned thighs constitute an effectual splint to the entire body, so the flexion necessary for turning cannot be obtained.

But, fortunately, this is the type of breech that is least troublesome, and least dangerous. The ease with which a frank breech often delivers may give a false sense of security about breech deliveries in general. The baby sits squarely over the cervix, the buttocks making an effectual stopper against cord prolapse, while the cervix is sufficiently dilated by the combined diameters of the baby's pelvis and thighs. I wish to emphasize the importance of these combined diameters, for complete cervical dilatation. Birth may be entirely spontaneous.

Now let us consider the group successfully turned:

VERSION SUCCESSFUL IN 160 OF 190 CASES, OR 84 PER CENT

When done	30th to 32nd week	7	(4 were turned during labor)
	32nd to 36th week	119	
	36th to 40th week	34	
		<hr/> 160	
Required a second turning	19		
Required a third turning	5		
Required a fourth turning	0		
Resulted in spontaneous vertex delivery		133	
Forceps delivery		19	
Podalic version for prolapsed cord		1	
Cesarean section		7	
		<hr/> 160	
Complications:			
Persistent occipitoposterior		8	
Face or brow presentation		0	
Prolapsed cord		1	
Other cord complications		0	
Premature separation of placenta		0	
Labor induced by version		0	
Weight of babies:			
Over nine pounds		27	
Between eight and nine pounds		40	
Less than five pounds		1	
Babies delivered as vertex and lost		3	
1. Mother chronic nephritic; 9½ pound baby; difficulty in extracting shoulders; death from birth injury.			
2. Died 40 hours before delivery; intrauterine <i>Cl. Welchii</i> infection; mother survived; reported in 1945.			
3. Macerated; fetal heartbeat absent from one week prior to a single version.			
Infant mortality:			
In 190 cases, four, or 2 per cent.			
If corrected by omitting cases 2 and 3 above, the rate would be 1 per cent.			
Maternal mortality	0		

In counting spontaneous deliveries, episiotomies were not considered as operative interference. A forceps delivery means some degree of dystocia.

Attention is called to the absence of cord complications. It is our belief that, in doing an external version, one is avoiding cord complications, rather than inviting it, because we are substituting a single pole, the head, for a double pole, the feet. Surely, the double pole is the more liable to entanglements.

Gentleness in manipulation is believed to account for the absence of placental disturbance and induction of labor. Strenuous effort is unwise and unnecessary. Anesthesia is dangerous.

In our breech group of 190 cases, the percentage of change after the thirty-fourth week was found to be higher, for no apparent cause:

Vertex to breech	35th week	5
	36th week	4
	37th week	1
	38th week	2
		<hr/>
		12

So the combined groups, totaling 1,190 cases, showed that only 19 spontaneously changed presentation after the thirty-fourth week, which is 1.6 per cent. This corresponds closely to the findings of Weisman¹ who followed 100 unselected cases by x-ray.

If spontaneous change mainly ceases at the thirty-fourth week, the preceding fortnight should be the optimum time for correcting faults. Siegel³ gives the thirty-second to the thirty-sixth week as the best time for external version.

Unlike presentation, position changes frequently, right up to term.

In analyzing the breech group, we counted as a breech every case found in breech presentation after the thirty-second week, omitting multiple pregnancies. The series includes the fifty-eight cases reported to the Virginia State Society in 1935.

In general, it is our policy to try to correct all faulty presentations by the thirty-fourth week of pregnancy. Before the thirty-second week, our experience indicates that spontaneous change is so common that interference is impracticable. Within this two-week period, thirty-two to thirty-four weeks, the baby appears small enough to be turned with fair ease, yet large enough to maintain its presentation when turned.

The technique of external version is extremely simple. When presentation and position have been definitely determined, with aid of x-ray when there is doubt, the most important requisite is gentleness. Abdominal muscles must be relaxed. Then slight but steady pressure applied to the poles in the right direction carries the buttocks upward and the head forward and downward in increased flexion.

Before taking up the 160 successfully turned, let us note a few things about the 30 that were not turned:

BREECH CASES THAT WERE NOT TURNED

Correctly diagnosed, external version tried and failed		25
Wrongly diagnosed, and no version attempted		5
Proved to be	Footlings	2
	Full breech	3
	Frank breech	16
	Type unrecorded	9
		<hr/>
		30

Of this last 9, the records show that one was a cesarean, 8 were spontaneous except for episiotomies, and all babies lived. So, for reasons given later, it seems fair to assume that most of them were of frank type. At any rate, the predominance of frank breeches among the cases where external version failed, was pronounced.

Longest labor, 27 hours. Frank breech, 10 pound baby.

Infant mortality, one. Full breech decomposed, 9½ pound baby; probably a section should have been done for disproportion.

That the frank breech is definitely the most difficult to turn, is in accord with the findings of Ryder,² Siegel and McNally,³ and Watson.⁴ The extended

In labor, the footling is far more hazardous than the other types; for it, we recommend the early use of a large dilating bag, as a safety measure.

The frank and full breech types are most safely delivered by conservative management, simple episiotomy and assistance to shoulders and head after the baby is half born.

In every case coming to delivery as a breech, x-ray determination of the exact type is highly important. The type of breech, as well as the relative size, must be known at the onset of labor, for safe management.

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In further reference to the delivery of breech cases, it is my belief that 90 per cent of the difficulties with breech births in general occur with footlings, either as primary footlings, or because another type was converted into a footling by operative means. With no disproportion, serious trouble threatens from one of two things, prolapse of the cord, or incomplete dilatation of the cervix. Both are major complications.

When a foot or leg is below the buttocks at the onset of labor, the irregular shape and small size of the presenting part causes early rupture of membranes, and allows space for the cord to work down; the cervix has such an irregular cork, or stopper, that the cord can easily prolapse; and cervical dilatation proves insufficient, because the baby's pelvis and thighs came through it separately.

In my opinion, this is a clear indication for a dilating bag. If, when the cervix is open 2 to 3 cm., a No. 6 Voorhees bag is introduced, it will hold back both cord and legs until dilatation is sufficient for quick and safe delivery. Nothing smaller than a No. 6 bag should be used. Effort is made to keep membranes intact, a two-pound weight is attached, and Demerol and scopolamin are given freely. Kosmak⁵ and Irving and Goethals⁶ employ bags for "selected" cases of breech labor, but they do not specify for which particular type.

For the same reason, when one brings down the legs of a full or frank breech, a comparatively safe type is converted into a dangerous type. We need to be more cautious about decomposing to speed delivery, as pointed out by Gordon, Garlick, and Oginz,⁷ Ware, Winn, and Schelin,⁸ Bill,⁹ Hansen,¹⁰ and Guyer and Heaton.¹¹ Gordon, in a study of three thousand breech deliveries, demonstrated that interference with normal mechanism, and rapid extraction, is the real cause for fatal outcome in many cases. I confess I am not able to tell, always, whether a cervix is completely dilated and paralyzed, or not. Trouble with the cervix has been encountered, when dilatation was thought to be absolutely complete. Goethals,¹² who, with Irving, advocated decomposition at full cervical dilatation, reported a fetal mortality of 5 per cent.

We need to think, and consider very carefully, before proceeding with decomposition. Fearing disproportion, in spite of negative x-ray evidence, we develop impatience and an urge to do something. But unless the baby or mother shows distress, it appears safer to allow more than the traditional two hours in second-stage labor, relieving pain by analgesics, and giving supportive intravenous treatment as indicated. We need to think more about the advantage of those upturned thighs in the mechanism of labor. The advantage is real.

Summary

One thousand unselected charts and the records of one hundred ninety breech cases indicate that in 98 per cent of cases the fetus has assumed its final presentation by the thirty-fourth week of pregnancy.

External version is a safe and easy maneuver.

The optimum time for version is between the thirty-second and thirty-fourth weeks.

In a series of 190 breech cases, version was successful in 84 per cent, with an uncorrected fetal mortality of 2 per cent.

Failures were mostly due to the extended legs of the frank breech.

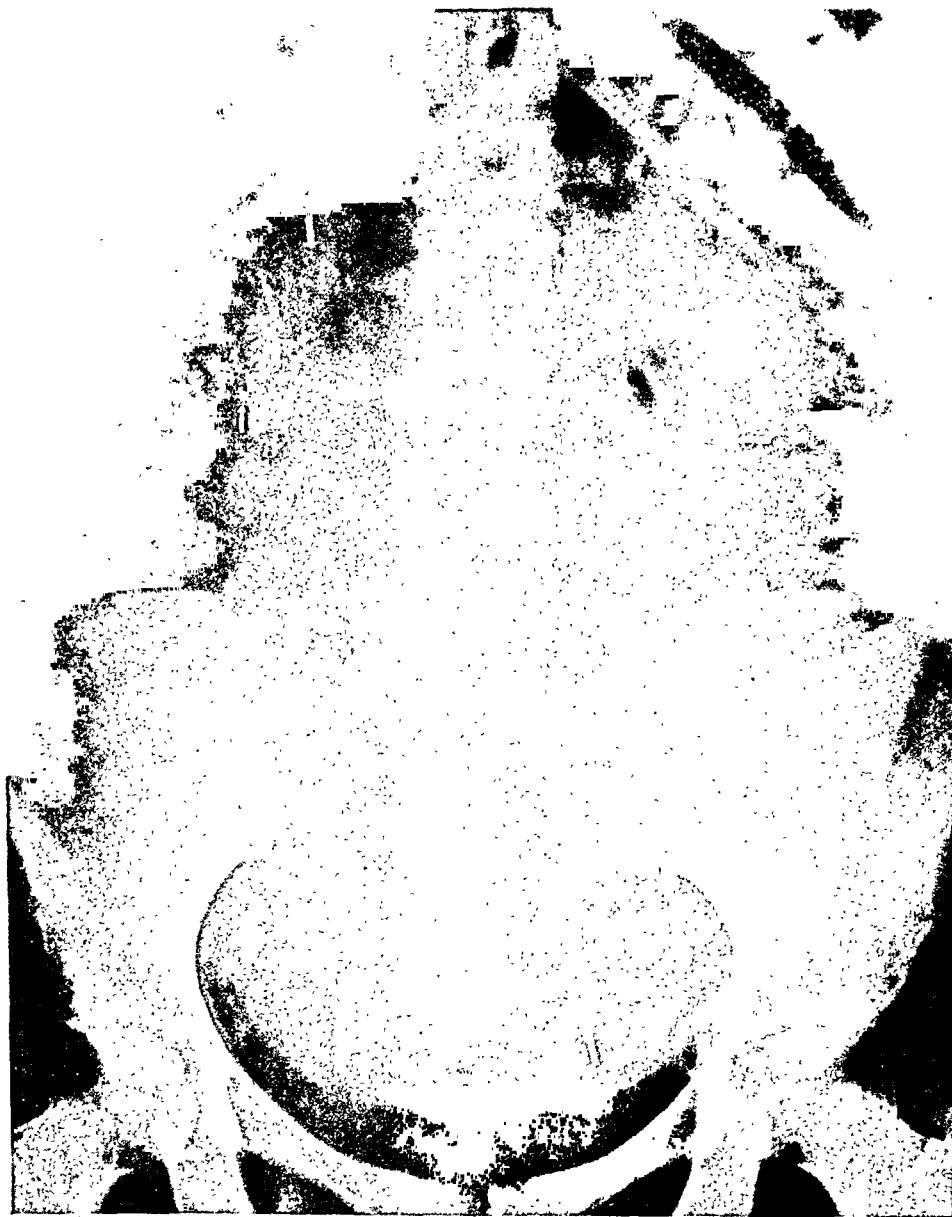


Fig. 1.—X-ray at 17 weeks' establishing early diagnosis of quadruplets. The long bones and spines are more visible than the skulls.

Summary

1. Quadruplet pregnancy occurs about once in 550,000 pregnancies.
2. This case reported was correctly diagnosed at approximately 17 weeks of gestation, by a combination of clinical and x-ray findings, apparently the earliest diagnosis on record.
3. Delivery of small, premature infants of a multiple pregnancy can usually be accomplished through the pelvic canal. Uterine inertia and cervical dystocia from postoperative scar tissue necessitated delivery by cesarean section in this case, apparently the second on record.

QUADRUPLLET PREGNANCY: DIAGNOSIS AT SEVENTEEN WEEKS OF GESTATION*

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THIS instance of quadruplet pregnancy merits reporting notably because it appears to be the earliest positive diagnosis on record. The diagnosis was established by a combination of clinical observations and x-ray studies, seventeen weeks after the first day of the patient's last preceding menstrual period. The case was successfully concluded at approximately thirty-one weeks by the delivery by cesarean section of living quadruplets, one male and three females, apparently being the second on record of delivery by section.¹

Multiple pregnancy was tentatively diagnosed by Dr. Hartman, when palpation during the early weeks of pregnancy showed excessive uterine enlargement. The patient's last menstrual period began on July 12, 1947. Nearing the seventeenth week the fundus of the uterus was slightly below the level of the lowest ribs, and she was referred by Dr. Hartman for x-ray on Nov. 7, 1947, exactly seventeen weeks from the first day of the last menstruation. Dr. Feightner's report is quoted verbatim: "Anteroposterior and lateral radiographic examination of the abdomen reveals the presence of four fetal skulls and vertebral columns in this abdomen. These fetuses are of approximately five months' gestation. The height of the fundus is at the lower border of the first lumbar vertebra. No other abnormalities are noted."

The anteroposterior film is reproduced herewith without retouching, but the diagnostic points are, regrettably, much less evident than in the original film seen in a viewing box. This is understandable, however, because the centers of ossification of a fetus are usually not clearly visible until about the eighteenth week, or the middle of a pregnancy.

Subsequent x-rays taken on Dec. 31, 1947, and Jan. 30, 1948, distinctly show the quadruplets and their relative positions.

On Feb. 14, 1948, namely, at thirty and one-half weeks from the beginning of the last period, the patient's membranes ruptured spontaneously, and a few hours later mild uterine contractions began.

A secondary trachelorrhaphy had been done on this patient in 1946, three years after her first pregnancy and delivery in 1943. It had been decided in an antenatal consultation, however, to subject her to a test of labor in this present delivery because the cervix seemed soft. After about seven hours of weak labor pains, the cervix was dilated to a stiff, sharp-edged ring about 3 cm. in diameter without progressive increase for several of these hours. On the indications of long-ruptured membranes (fourteen hours), primary uterine inertia, and cervical dystocia from scar tissue, cesarean section was performed by Dr. Titus, using the lower uterine segment (Kerr-Phaneuf technique) type of section.

The first infant, the male, had a single, separate placenta; the other three (females) had a single large placenta with separate amniotic sacs and a single chorion.

All were vigorous, though small (each slightly more than 3 pounds, or 1,361 Gm.) and obviously premature. All have survived to date and are growing well. They have been given repeated pediatric consultations by Dr. Richard R. O'Toole of Pittsburgh.

The patient's recovery was uneventful.

*Presented before the Pittsburgh Obstetrical and Gynecological Society, April 5, 1948.

A RUPTURED ABDOMINAL PREGNANCY WITH MASSIVE, RAPID TRANSFUSIONS AND UNCOMPLICATED RECOVERY

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THE great amount of blood given to this one patient, and the rapidity of its administration, impelled us to report this case. The survey of recent literature, including studies conducted during World War II, reveals no instance of an individual surviving after being given 7,500 c.c. of whole blood within a six-hour period.²⁻⁶ It is axiomatic that, in general, severe blood loss must be replaced at a rate dependent upon the speed of hemorrhage. Practically the only exceptions are cases with pulmonary or intestinal injuries.

Case History

G. C., a 25-year-old, para 11001, was first seen at the Sinai Obstetrical Clinic Sept. 9, 1947. Records later obtained from the Baltimore City Hospital stated that the patient was seen by them in this same pregnancy May 28, 1947, when she gave the history of spotting associated with crampy lower abdominal pains on April 1, May 8, and May 28. Her last menstrual period was Jan. 20, 1947, and the estimated date of confinement Oct. 27, 1947. Obstetric history revealed that she had had an uneventful breech delivery of a seven pound, two ounce infant at another hospital in 1941. Examination, September 9, also showed a breech presentation, blood pressure 98/60, and hemoglobin 74 per cent. The patient was given a return appointment for September 30, but on September 25, at 9:30 A.M., the husband called to state that his wife was having severe abdominal pain following a gentle bump. He had slipped on a crayon and the point of his elbow collided with his wife's abdomen. This was immediately followed by pain of such severity that she could not move. Patient was brought by ambulance to the accident room at 10:30 A.M. She was in obvious shock and complained of severe abdominal pain, worse in the right upper quadrant. Her blood pressure was 70/50, pulse 130. The upper abdomen was tense, more markedly so on the right; pressure in the right upper quadrant caused severe pain. The lower abdomen was comparatively soft, and an irregular area in the region of the umbilicus could be made out. Percussion elicited dullness in both flanks. The fetal heart was heard to the left of the umbilicus. Because of the rigidity of the abdomen, small parts could not be palpated. A diagnosis of ruptured uterus was made by the resident obstetric staff, the patient was cross-matched with Rh-positive, type A blood, and a 500 c.c. transfusion was started immediately. A consultant from the senior staff confirmed the diagnosis and the patient was immediately taken to the operating room where, under cyclopropane anesthesia, the abdomen was opened through a right rectus incision. The peritoneum was tense and discolored; when it was incised, approximately 1,500 c.c. of blood and clots escaped. The fetus was found lying free in the peritoneal cavity and was easily delivered. The cord which was very short was torn from its attachment to the placenta by this manipulation. Examination revealed that the uterus was intact, soft, and enlarged to approximately a three to four months' pregnancy. The placenta and membranes were attached to the right adnexa below, omentum above, parietal peritoneum to the right and laterally, and it was believed at this time that there was an attachment to the intestines posteriorly. It was decided not to disturb the placenta and a 4 inch rent, situated to the left and anteriorly through which the baby had been extruded from the sac at the time of its rupture into the abdominal cavity, was sutured. Hemostasis was reinforced by placing Oxycel gauze over this sutured tear in the placenta. As the peritoneum was being closed, an ooze of bright red blood was noticed in the right gutter. The exact site of this bleeding was not determined but it was believed to be from a slight separation of the placenta during delivery of the baby. This region was packed with Oxycel gauze but complete hemostasis was not obtained. The abdomen was then closed with the belief that the Oxycel gauze and a tight binder would control oozing. The 4



Fig. 2.—X-ray of quadruplet pregnancy at about twenty-eight weeks.

4. The survival rate of quadruplets is low. These infants are living and thriving. They were under incubator care for their first several weeks of life.
5. The pregnancy consisted of a single fetus (male), and identical triplets (females).

Reference

1. Ullery, J. C.: J. A. M. A. 128: 183, 1945.